INDEX NUMBER
Section 1

Paid Circulation, 35,158

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 252 • JUNE 30, 1955 • NUMBER 26

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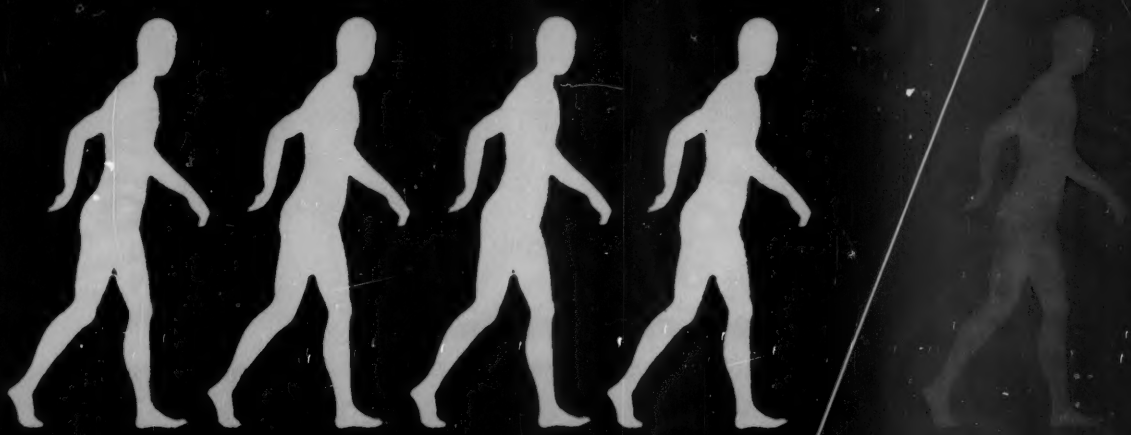

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1. Winsor, T., Humphreys, P.: Angiology *3*:1 (Feb.) 1952.
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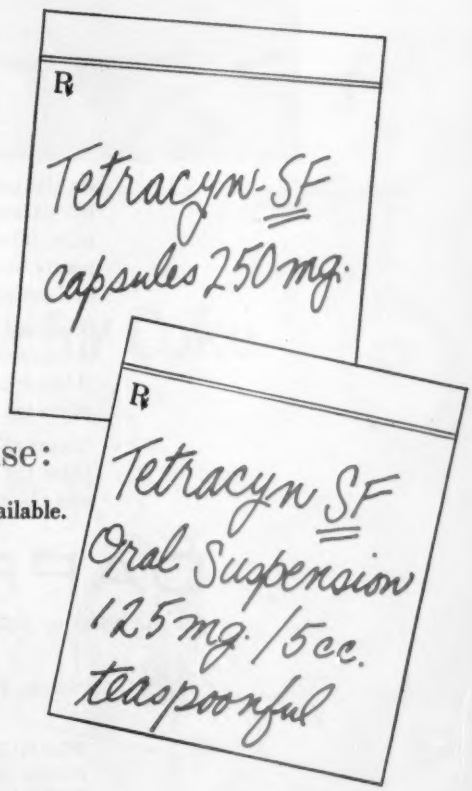

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1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952.
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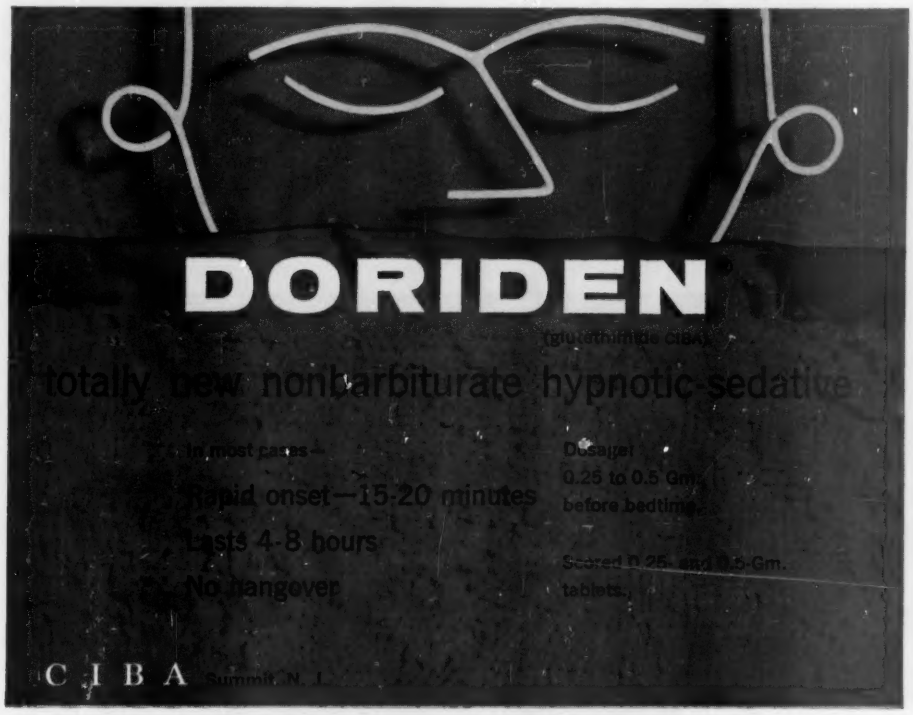

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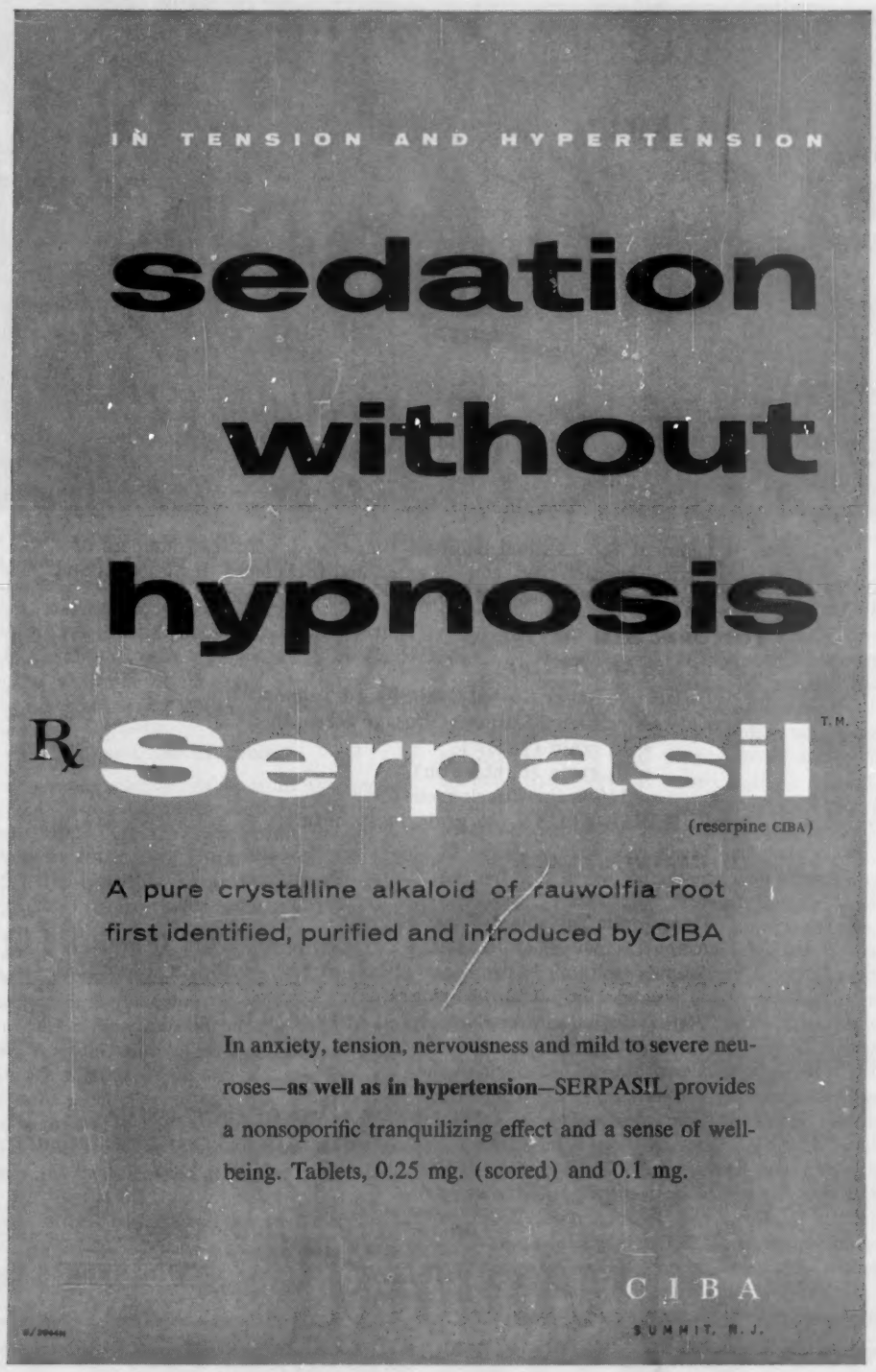
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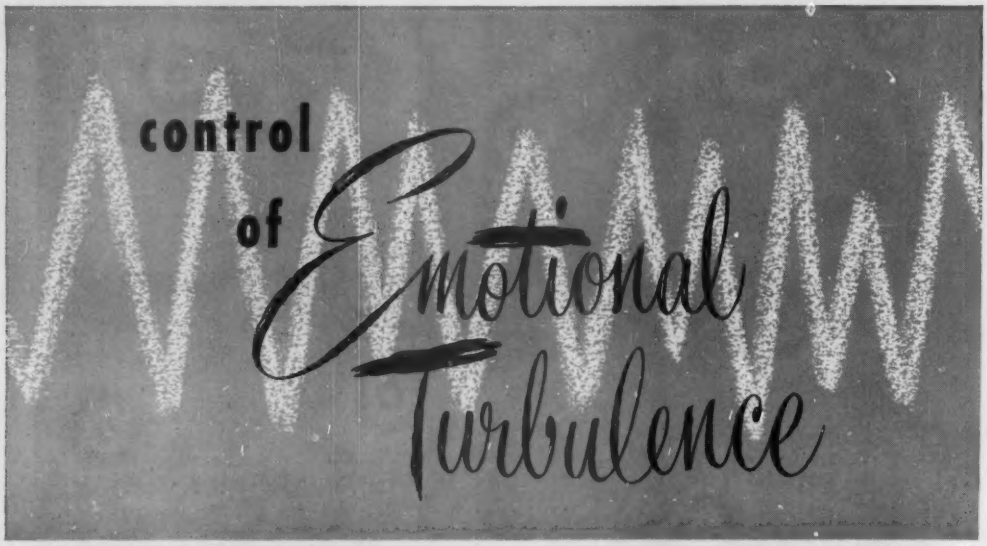

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Volume 252 JUNE 30, 1955 Number 26

OCCURRENCE OF GASTRIC CANCER AMONG PATIENTS WITH PERNICIOUS ANEMIA AT THE BOSTON CITY HOSPITAL*

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BOSTON

ALTHOUGH it is generally recognized that gastric cancer occurs with increased frequency in patients with pernicious anemia,[1-3] reported rates vary widely from a low of 0.16 per cent[4] to a high of 14.9 per cent.[5] Differences in the sampling methods, the relatively small number of patients with pernicious anemia available at any one clinic and the differing criteria utilized for the diagnosis of pernicious anemia contribute to the disparity among these figures. Many patients with pernicious anemia are seen at the Boston City Hospital every year. To assess the practicality of routine screening of these patients for gastric cancer it was necessary first to establish the frequency.

MATERIAL AND METHODS

Diagnostic index files available from the general wards of the Boston City Hospital, the Outpatient Department, the Thorndike Memorial Laboratory and the Mallory Institute of Pathology provided 1222 names of patients with "pernicious anemia" diagnosed between 1915 and 1951. Observations were recorded on 658 of these patients by a group of physicians investigating the pathogenesis of pernicious anemia at the Thorndike Memorial Laboratory. Patients were usually seen by members of this group on the general wards of the hospital, transferred to the Thorndike ward for study, and then followed in the Outpatient Department. Because of this investigative orientation strict criteria were employed for making the diagnosis of pernicious anemia in these patients. These criteria have been reviewed recently by Castle[6] and included the following: macrocytic anemia; achylia gastrica; a characteristic reticulocyte response to specific antianemia therapy provided by several substances, including extracts of beef and pork liver, muscle and stomach given parenterally alone or orally in combination with human gastric juice (in more recent years, highly purified preparations of vitamin B_{12} have been utilized); the characteristic clinical findings of glossitis and of subacute combined degeneration of the spinal cord, which were often observed; megaloblastic bone marrow, providing confirmatory evidence in many patients; and gastric atrophy, observed gastroscopically in some cases.¶

We accepted without review all diagnoses of "pernicious anemia," with the exception of patients regarded as having both gastric cancer and pernicious anemia; these were reviewed individually. Of the original 1222 patients 75 had diagnoses recorded of both "pernicious anemia" and "gastric cancer." Only 28 of these, however, were sufficiently well documented or satisfied our criteria well enough to be accepted for this study. Twenty-one of these were among the 658 "Thorndike" patients. It is likely that a number of patients with both diseases escaped notice, since we did not review all 1222 records of patients with "pernicious anemia" for unindexed diagnoses of "gastric cancer"; nor did we review the even more numerous records of patients with proved gastric cancer for unindexed diagnoses of "pernicious anemia." The diagnosis of "gastric cancer" was accepted only when confirmed by the specific diagnostic measures. The lesion was seen grossly at autopsy in 14 patients and at laparotomy in 11 others. The remaining 3 had unequivocal clinical and x-ray evidence of gastric cancer.

During the course of the study, the importance of morphologic confirmation of the clinical diagnosis of gastric cancer became increasingly apparent. Thus, patients with typical clinical histories suggesting gas-

*From the Mallory Institute of Pathology, the Second and Fourth Medical Services (Harvard), and the Thorndike Memorial Laboratory, Boston City Hospital, the Department of Pathology, Boston University School of Medicine, and the Department of Medicine, Harvard Medical School.

Supported in part by a research grant (C-2090) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

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¶With increasing knowledge the criteria for the diagnosis of pernicious anemia at this laboratory have constantly become more strict. Thus, a few of the earlier accepted diagnoses would probably now be reclassified as the anemia of folic acid deficiency. In 1927 exact diagnosis of pernicious anemia was first made possible by the discovery of the reticulocyte response to specific therapy. A number of patients in the present study were seen before that date, and none had gastric cancer (see Table 3).

tric cancer, including recent upper gastrointestinal symptoms, weight loss, occult blood in stools and apparent x-ray confirmation of gastric neoplasm, were sometimes shown at surgery or autopsy not to have gastric cancer. For example, J.M., a fifty-four-year-old woman, was admitted to the hospital with symptoms of weakness for two years, diarrhea for one year and one month of nausea and vomiting. The blood findings were consistent with those of pernicious anemia in relapse. The patient responded to liver extract, but vomiting persisted. X-ray examination showed a constant irregularity of the gastric antrum consistent with carcinoma, and the patient was discharged to a chronic-disease hospital with this diagnosis. Records at the second hospital, however, revealed that the intestinal symptoms were caused by adhesions of the upper gastrointestinal tract resulting from a hysterectomy performed twenty years before. No evidence of gastric cancer was found at autopsy. Another patient, B.S., a sixty-nine-year-old woman, was admitted to the hospital, where a diagnosis of pernicious anemia was established. Subsequently, because of anorexia, vomiting and weight loss, x-ray study of the upper gastrointestinal tract was performed in the Outpatient Department. This disclosed a large, irregular, constant, polypoid filling defect of the distal half of the antrum measuring 5.5 by 2.5 cm. Peristalsis did not pass through the distal half of the stomach. A diagnosis of cancer was made, but the patient refused exploration. Four years later, however, she was seen in the clinic without weight loss, anemia or blood in the stool, but retaining her epigastric symptoms. Again she refused further study. The diagnosis of gastric cancer made four years previously seemed no longer tenable and was discarded.

These and other cases leave no doubt that the diagnosis of gastric cancer when not confirmed pathologically must be supported by unequivocal clinical, laboratory and x-ray findings and, in addition, close follow-up studies. Few discussions of this problem have documented sufficiently clearly the diagnosis of gastric cancer.

In the present series only 3 cases were accepted in which anatomic proof of gastric cancer was not available. In each, however, clinical findings were confirmed by laboratory observations and radiologic diagnoses (which were "large carcinoma of lower third of stomach," "definite scirrhous carcinoma" and "multiple polypoid carcinoma," respectively). All patients died a few months after the diagnosis was made, and no other cause for death was apparent.

Pathology of Gastric Cancer

The diagnosis of "adenocarcinoma" was made 19 times, and "infiltrating" or "diffuse" 8 times; 2 polyps were described as having undergone "malignant degeneration," and 1 patient had multiple benign polyps in addition to an adenocarcinoma. The neoplasm was located in the body or fundus in 11 cases, as compared with 7 in the pylorus and antrum. This distribution conforms roughly to that noted by others.[7-13] In 174 patients, including the present cases, 69 neoplasms were found in the pylorus and antrum, and 87 in the body and fundus, and 22 were too diffuse to be localized. Since 40 to 75 per cent of cases of gastric cancer in patients without pernicious anemia are situated in the pylorus and antrum,[9,14] Torgersen[9] thought that the predominance of lesions elsewhere in the stomach in pernicious anemia was of special significance.

Characteristics of Gastric Cancer in Patients with Pernicious Anemia

Of our 28 patients with both diseases, 16 were males and 12 females. A predominance of males over females with gastric cancer without pernicious anemia was noted in 248 patients autopsied at the Mallory Institute of Pathology between 1933 and 1949, among whom males were 2.4 times as frequent as females. On the other hand, females were 1.5 times as frequent as males among pernicious-anemia patients without gastric cancer. If a mean ratio of males to females is calculated the figure 16.1:11.9 is determined. This is approximately the sex ratio found in our group of 28 patients with cancer. These figures suggest that gastric cancer in our patients with pernicious anemia has the same predilection for males as that in patients without pernicious anemia.

The patient's age at the time pernicious anemia was diagnosed varied from forty-one to seventy-eight years. The age at which gastric cancer was diagnosed in these patients varied from fifty-one to eighty, zero to fifteen years elapsing between the diagnosis of the two diseases. The interval averaged six and six-tenths years. Mosbech and Videbaek[2] recorded intervals averaging ten years for males, seven years for females and eight years for the entire group. In our patients an interval of one year or less was noted in 6 patients, and the diagnosis of both diseases was made at the same hospital admission several times; these data do not support the contention that prolonged duration of pernicious anemia predisposes to gastric cancer. Rather, the opposite contention may be raised — namely, that gastric cancer may precipitate the onset of megaloblastic anemia. To the extent that the cancer of the gastric fundus may obliterate functioning gastric glands, diminish gastric secretion and contribute to reduced food intake, this appears to be reasonable.

Figure 1 indicates the mean ages at death of samples of patients with pernicious anemia alone and gastric cancer alone. There has been a steady increase in age from approximately fifty years in 1930 to approximately seventy in 1950. Also indicated on the graph are the individual ages of patients with both gastric cancer and pernicious anemia. The graph helps one to understand why the apparent frequency of gastric cancer in patients with pernicious anemia

has been widely emphasized relatively recently. The diagnosis of gastric cancer was proved 10 times during the fifteen-year interval of 1925 to 1940 and 18 times in the subsequent twelve years. Before 1935 at this hospital relatively few patients with pernicious anemia survived long enough to get gastric cancer. In addition to improved therapy for pernicious anemia, transfusion, antibiotics and other advances have made this possible. The rise in average age of patients dying of gastric cancer in the past decade also reflects the increased longevity of the hospital population. It is apparent from the graph that gastric cancer threatens the young, as well as the elderly, patients with pernicious anemia.

Frequency of Gastric Cancer in This Series

The occurrence of gastric cancer in various subgroups is listed in Table 1. The highest occurrence

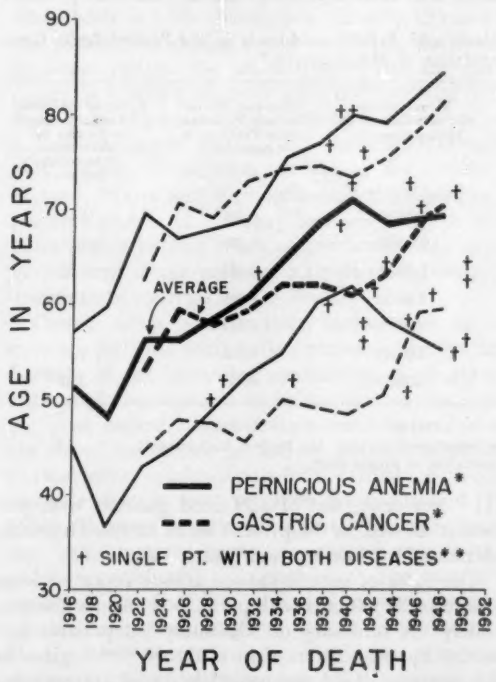

Figure 1. *Age at Death of Patients with Pernicious Anemia and Gastric Cancer.*

**Patients autopsied at the Mallory Institute of Pathology; average age at death each year bounded above and below by one standard deviation. The data are derived from the "Mallory" index files and include patients other than those who were studied in the pernicious-anemia group of the present series in addition to all patients who were studied.*

***Individual patients of the present series with both pernicious anemia and gastric cancer; age at which the patient died or was lost sight of and was presumed to be dead (25 patients).*

was found in the autopsy series, 11.9 per cent of the Thorndike cases and 6.5 per cent of the others. For purposes of comparison the rate of autopsied patients dying with gastric cancer but without pernicious anemia was found to be 1.9 per cent, and when corrected for the group fifty to seventy-nine years of age, this became 2.7 per cent. At the conclusion of the study (October, 1951) 241 patients were being treated for pernicious anemia in the Outpatient Department. Three (1.2 per cent) of these had gastric cancer. Of the 658 Thorndike patients, 278 had been lost to follow-up study, and 2 of these (0.7 per cent) were known to have had gastric cancer when last seen. Because of the short survival time after the diagnosis of gastric cancer, a high percentage of these patients can be followed until they die. The low rate of gastric cancer among the patients lost sight of and the high rate in the dead group may reflect this factor.

Table 1. *Occurrence of Gastric Cancer in 1222 Patients with Pernicious Anemia Seen at the Boston City Hospital from 1915 to 1951.*

Group	No. of Patients with Pernicious Anemia	No. of Patients with Gastric Cancers
Present series:		
Thorndike group only	658	21(3.2%)
Boston City Hospital without Thorndike group	564	7(1.2%)
Totals	1222	28(2.3%)
Autopsies:		
Thorndike group only	59	7(11.9%)
Boston City Hospital without Thorndike group	108	7(6.5%)
Totals	167	14(8.4%)
Thorndike group only:		
Known dead:		
Dead with autopsy	59	7(11.9%)
Dead without autopsy	80	9(11.3%)
Total dead	139	16(11.7%)
Not known dead:		
Alive in October, 1951	241	3(1.2%)
Lost sight of	278	2(0.7%)
Totals	519	5(1.0%)
Not known living (dead & lost sight of)	417	18(4.3%)

The apparently higher occurrence of cancer in the Thorndike group of autopsied patients with pernicious anemia as compared with the others cannot be explained with certainty. Because only patients with low hemoglobin values were accepted in transfer, the opportunity for exact diagnosis of pernicious anemia in the Thorndike ward was enhanced. Many patients in the other groups were admitted to the hospital for the first time without anemia but with other acute illnesses, the diagnosis of pernicious anemia being obtained by history. This diagnosis was usually made on clinical grounds by the family physician, who could not apply the confirmatory laboratory tests available in the Thorndike group. The institution of nonspecific antianemic therapy precluded subsequent

confirmation. Other patients admitted to the general medical wards either were too ill or died too soon to permit performance of discriminating diagnostic procedures; the diagnosis of pernicious anemia in such cases was necessarily presumptive. These factors undoubtedly increased the number of cases diagnosed as pernicious anemia among patients outside the Thorndike group without adding to the number of gastric cancers. Since we have no reason to assume that the diagnosis of gastric cancer was made with unequal accuracy in the Thorndike and general-hospital populations, the rate of gastric cancer cited for the former appears to be more reliable than that cited for the latter.

Reported Frequency of Gastric Cancer Among Patients with "Pernicious Anemia"

The prevalence of gastric cancer in patients with pernicious anemia reported in the literature varies widely. Unfortunately, not all reports describe the populations studied, and it is clear that some consist of mixed samples of living and dead patients. The importance of this factor is indicated in Table 1, in which, depending on the type of sample, our rate can be seen to vary between 0.7 per cent (for patients who were lost sight of) and 11.9 per cent (for those who came to autopsy). Norcross et al.,[3] in 1952, tabulated the over-all frequency of gastric cancer in patients with pernicious anemia from reports previously published and derived the figure of 1.17 per cent — a rate identical to that of their own series. A compilation of findings derived from 8492 living and dead patients with pernicious anemia reported by 20 authors[2-4,7,8,10,11,15-28] since 1923 yields an over-all prevalence of gastric cancer of 2.04 per cent. This is slightly lower than the figure of 2.3 per cent among the 1222 patients with pernicious anemia seen at the Boston City Hospital since 1915.

The apparent morbidity incidence of gastric cancer in the population of Massachusetts aged fifty to eighty-four years was calculated from data on vital statistics available at the Massachusetts Department of Public Health (Table 2) and was compared with that of a sample of 644 patients in the Thorndike group. Despite the paucity of data, the frequency of gastric cancer in the population with pernicious anemia was 1.07 to 14.81 times higher than that in the Massachusetts population age groups. The highest relative prevalence occurred in the younger age groups.

Mosbech and Videbaek,[2] in 1950, found that the life expectancy of patients with pernicious anemia did not differ significantly from that of patients without pernicious anemia. However, they found 15 (5 per cent) cases of gastric cancer instead of an expected 5.2 (1.7 per cent) among 301 patients followed over a ten-year period. Of the 115 who died 14 (12.2 per cent) died with gastric cancer. The authors concluded that the excessive mortality from gastric cancer was statistically significant. Sixteen patients (11.7 per cent) out of 139 dead patients with pernicious anemia in the present series at the Thorndike Memorial Laboratory had gastric cancer.

The rates of gastric cancer among reported series of autopsied patients with pernicious anemia compare closely. A summary of 950 autopsied patients presented by six authors since 1921[1,5,7,26,29,30] gives an average rate of 8.5 per cent. We found a gross prevalence of 8.4 per cent in 167 autopsies and 11.9 per cent in the 59 Thorndike autopsies alone. Norcross et al.[3] suggested that the autopsy rate of 12.3 per cent given by Rigler, Kaplan and Fink[22] was erroneously high because of the method of calculation. An even higher figure (14 per cent) was derived by Hyland, Watts and Farquharson,[30] who excluded 51 patients who died of pernicious anemia alone from their total of 102 autopsied patients. They reasoned that death from pernicious anemia properly excluded patients from the potential cancer group.

The 11.9 per cent rate of gastric cancer shown in the autopsied Thorndike group was somewhat less

Table 2. *Morbidity Incidence of Gastric Cancer among 644 Patients with Pernicious Anemia in the Present Series Compared with That in the General Population of Massachusetts.**

Age Group	Patient Years Among Patients with Pernicious Anemia in Present Series	Cases of Gastric Cancer Among Patients with Pernicious Anemia	Mortality of Gastric Cancer in Massachusetts	Morbidity of Gastric Cancer in Massachusetts†	Expected No. of Cancers in Group with Pernicious Anemia‡	Ratio of Observed to Expected Cases of Cancer in Group with Pernicious Anemia
yr.						
50-54	449	2	0.00022	0.00030	0.135	14.81
55-59	543	4	0.00048	0.00066	0.358	11.17
60-64	618	6	0.00069	0.00095	0.587	10.22
65-69	613	2	0.00110	0.00150	0.919	2.18
70-74	550	5	0.00170	0.00231	1.271	2.94
75-79	330	1	0.00209	0.00284	0.936	1.07
80-84	139	1	0.00233	0.00317	0.421	2.37

*Data from Division of Vital Statistics of Office of Secretary of Commonwealth 1944-49.
†To calculate morbidity, mortality multiplied by 1.36 (according to personal communication from Dr. Herbert L. Lombard).
‡To calculate expected number of gastric cancers in this group, morbidity multiplied by patient years.

striking when compared with that in other autopsy series. In 10,566 autopsies done on men and women over twenty years of age Lummerich,[31] in Hamburg, found that gastric cancer was responsible for 5 per cent of the deaths of women between forty and seventy years and 8.8 per cent of the deaths of men between fifty and seventy years of age. Hyland et al.,[30] however, reported a figure of only 3 per cent for gastric cancer in 3000 consecutive autopsies, unclassified for age, at the Toronto General Hospital.

In the present series, of the 52 autopsied patients with pernicious anemia but without gastric cancer, 37 died either in their first episode of acute anemia or in subsequent relapse. In 18 of these no cause of death was found at autopsy other than pernicious anemia. The remaining 19 died during acute relapse or during the first episode, and death was caused in part by an unrelated second disorder, such as congestive heart failure, pulmonary embolism, cerebral thrombosis or lobar pneumonia. In only 15 cases did the patients die during remission. When patients die in acute relapse the proportionate risk for gastric cancer is reduced. Accordingly, the potential occurrence rate of gastric cancer among our patients with pernicious anemia may actually have been considerably higher. Thus, with the use of the method of Hyland, Watts and Farquharson,[30] the figure of 17 per cent gastric cancer may be derived if one eliminates patients dying solely of pernicious anemia and 32 per cent if one excludes all patients whose acute anemia was contributory to death.

On the other hand, certain factors tend to concentrate patients with both diseases in the hospital. Because of the increasing availability of proprietary antianemic medications more patients each succeeding year escape hospitalization entirely, and many are never recognized as having pernicious anemia. Furthermore, sudden death from cardiac or cerebrovascular disease may preclude hospitalization. Reliable diagnoses of these disorders when they supervene can sometimes be made without hospitalization, and such patients may die elsewhere. The protracted symptoms associated with gastric cancer, however, tend eventually to bring the patient to the hospital. Thus, gastric cancer is likely in a higher percentage of hospitalized than in unhospitalized patients with pernicious anemia.

The average age at death of patients with pernicious anemia in this series has steadily risen during the past three decades, and it is reasonable to assume that more patients survive long enough to acquire gastric cancer (Fig. 1). These factors undoubtedly contribute to the apparently growing frequency of cases, and it is likely that a still larger number of gastric cancers in hospitalized patients with pernicious anemia may be expected in the future.

It is unlikely that the true frequency of gastric cancer in patients with pernicious anemia can ever be determined for the many reasons discussed above. Pernicious anemia or vitamin B_{12} deficiency is not always a clinically obvious disorder. Advancing age tends to increase the susceptibility to deficiency of "intrinsic factor" and dietary vitamin B_{12}, and reduced absorption of vitamin B_{12} from the gut. Unless all these factors operate seriously in the patient's disfavor acute anemia may not develop. Nevertheless, even those who never acquire acute anemia may be equally susceptible to gastric cancer if gastric atrophy is, in fact, a premalignant condition as many workers suggest.[1,7,32,33]

The present study does give a working estimate of the number of hospitalized patients with overt pernicious anemia in whom gastric cancer may eventually develop. Its principal importance may lie in calling attention to a group of patients with gastric atrophy years before the onset of gastric cancer. It is hoped that study of these patients may provide clues to the difference between patients destined to have gastric cancer and those patients who will remain free of it.

Risk of Gastric Cancer in Pernicious Anemia

Figure 2 *A* and Table 3 show the total number of patients with pernicious anemia seen by the Thorndike group in each year since 1918. The annual number of patients observed by the study group increased steadily to more than 240 in 1945. Patients alive in any year but who are known to have died before October, 1951, are indicated in the lowest segment of the bar in Figure 2*A*, those still living in October, 1951, by the upper segment, and those lost sight of by the middle segment. For example, of 179 patients seen in 1938, 64 were still living in October, 1951, 45 were dead, and 70 had been lost sight of. It is likely that a large percentage of the patients lost sight of died within a short period thereafter.

Figure 2*B* and Table 4 present the annual number of patients with pernicious anemia in whom gastric cancer eventually developed. There was an increase in the number of patients each year—from 1 in 1927 to 12 in 1938—who either had gastric cancer in that year or subsequently had it. Before 1938 not more than 1 patient with pernicious anemia was known to have gastric cancer during any single year. In 1950, 3 patients died of gastric cancer, and 1 other was still living with the disease. Thus, a steady increase in the patients with pernicious anemia destined to die of gastric cancer coincided with the increasing size of the group studied.

These data permit an estimate of the size of the reservoir of patients with pernicious anemia who are destined to get gastric cancer. Since it is possible to assign a patient to this cancer reservoir only in retrospect, the estimates must be considered to be minimal. The reservoir will be increased as additional cases of gastric cancer develop. Of 179 patients with pernicious anemia seen in 1938, for example, 2 died of gastric cancer in that year (solid circles in Fig. 2*B*), and 10 others eventually manifested gastric can-

cer ("X's" in Fig. 2*B*). Two of the 70 patients who lost contact with the clinic were known to have died of gastric cancer. Of the 64 patients still living, 1 had gastric cancer. If one were to assume that no more

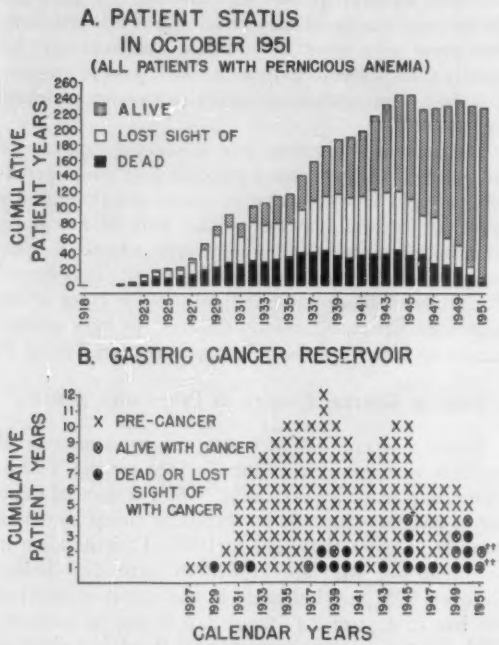

FIGURE 2. *Patients with Pernicious Anemia Seen by the Thorndike Group Each Year (Total of 658 Patients) from 1918 to 1951* (A) *and Number of Patients Each Year (Total of 21) in Whom Gastric Cancer Had Developed by 1951* (B).

The part of the patient group seen in any year and alive in October, 1951, is indicated by the dotted square, the part seen in any year and lost sight of by October, 1951, and presumed to be dead, by the white square, and the part seen in any year and known to have died by October, 1951, by the black square (A).

The letter "X" indicates the year in which gastric cancer developed at some time before October, 1951, in a patient seen at this clinic as having pernicious anemia, the diagnosis of cancer not yet having been made, the circled "X" the year in which a patient with pernicious anemia was known to have gastric cancer and was still living, and the solid circle the year in which a patient known to have gastric cancer died or was lost sight of and presumed dead (B).

†*Patient lived five years after surgery was performed in 1945 and was assumed to be cured; a solid circle was not drawn for this patient, and he occurs in the graph only once as a circled "X".*

††*Patient died within a year of the completion of this study.*

cases of gastric cancer would appear after 1951, an absolute minimum figure of 12/179 (6.7 per cent) incidence of gastric cancer would be obtained for the group of patients seen in 1938. The assumption that the remaining living patients with pernicious anemia would all remain free of gastric cancer is unreasonable, since several studies have indicated a rate in groups of living patients with pernicious anemia of approximately 1 or 2 per cent at any one time.

If one defines the gastric-cancer reservoir among patients with pernicious anemia as the prevalence of cancer in patients who have completed their life span, one may calculate this reservoir from our data as follows (Table 4): of the patients seen in 1938, 45 had died by October, 1951, and 70 had been lost sight of (presumed dead); 12 (10.4 per cent) of this group were known to have had gastric cancer, including 1 living patient whose lesion was surgically removed in 1945. From an average of the reservoir for the peak years 1933 to 1938 the figure of 10.2 per cent of gastric cancer is derived; with the years 1933 to 1949 as an average the figure of 8.7 per cent is derived.

SCREENING OF PATIENTS WITH PERNICIOUS ANEMIA

The high rate of gastric cancer among patients with pernicious anemia raises the question of the routine use of screening procedures. The physician who accepts the principles of routine screening for all patients with pernicious anemia commits himself and

TABLE 3. *Patients with Pernicious Anemia Seen Each Year by the Thorndike Group from 1918 to 1951 (Total of 658 Patients).*

YEAR	STATUS AS OF OCTOBER, 1951			
	PATIENTS DEAD	PATIENTS ALIVE	PATIENTS LOST SIGHT OF	TOTAL PATIENTS PER YEAR
1918	1	—	—	1
1919	—	—	—	—
1920	—	—	—	—
1921	1	—	—	1
1922	2	—	2	4
1923	6	1	6	13
1924	11	2	7	20
1925	10	2	10	22
1926	13	4	7	24
1927	14	4	16	34
1928	20	7	26	53
1929	23	11	41	75
1930	29	16	46	91
1931	27	17	35	79
1932	31	23	48	102
1933	30	28	47	105
1934	33	34	47	114
1935	37	38	44	119
1936	42	44	55	141
1937	42	51	66	159
1938	45	64	70	179
1939	39	70	78	187
1940	36	77	77	190
1941	39	84	75	198
1942	40	95	82	217
1943	41	113	78	232
1944	45	124	75	244
1945	39	133	72	244
1946	32	138	57	227
1947	28	150	50	228
1948	27	168	35	230
1949	24	186	28	238
1950	13	204	13	230
1951	7	219	2	228

his patient to a program of many years' duration. In our series the average duration of pernicious anemia before the onset of gastric cancer was approximately seven years (eight years in the series by Mosbech and Videbaek[2]). Since 90 per cent of the patients will never have gastric cancer, unselected screening of them would be performed for the remainder of their lives. For patients seen in this clinic, this would amount to at least twelve years. Furthermore, since gastric cancer appears to metastasize early, it is doubtful whether annual screening would save many

lives. The ideal screening method must be simple and inexpensive enough to permit more frequent repetition—for example, at intervals of three to six months. This frequency of examination limits screening procedures to those least expensive and most easily performed. The expense of the standard x-ray method and the need for close professional administration seriously limit its use as a screening technic. Gastroscopic screening, perhaps the most effective means for diagnosing polyps of the stomach—considered by most pathologists to have malignant potential—requires the services of highly trained physicians.

For these reasons we propose the following program: routine stool examinations for occult blood at monthly intervals; examination of gastric cytology at intervals of three to six months; and follow-up x-ray and gastroscopic study in suspicious cases.

The reports of Cooper and Papanicolaou,[34] Graham[35] and Rubin et al.[36] have clearly demonstrated the accuracy of the cytologic method. The patient with pernicious anemia is an ideal subject for cytologic study because the absence of acid peptic juice permits the recovery of exfoliated cells in a good state of preservation. Although the abrasive-balloon[37] and Ayre-brush[38] modifications of the method provide larger numbers of cells simple gastric lavage through an ordinary stomach tube[35] is the most practicable for routine office screening. A small quantity of saline solution is forcibly injected into the stomach, withdrawn and reinjected several times. The collected aspirate is promptly centrifuged at high speed for twenty or thirty minutes, and smears of the sediment are immediately fixed in equal parts of 95 per cent ethanol and anesthetic ether. The fixed slides may be sent for staining and interpretation to a reputable laboratory. Both the guaiac test and the simple method of aspiration cytology may be performed by technicians with minimal professional supervision.

These observations emphasize the importance of exact criteria in the diagnosis of pernicious anemia and, in the unproved cases, may justify withholding parenteral and antianemic therapy until appropriate diagnostic studies are completed.

Graham and Rheault[39] and Massey and Rubin[40] have described cells in gastric smears that appear to be characteristic of gastric atrophy in patients with pernicious anemia. Thus, the cytologic method may have the added advantage of permitting an indirect confirmation of the diagnosis of pernicious anemia even in adequately treated patients. Persistent absence of these characteristic cells on repeated examination raises doubt of the validity of the diagnosis of pernicious anemia and may preclude the need for further screening or, in fact, for further therapy for pernicious anemia. Further study is needed of this matter, as well as of the unconfirmed suggestion of Massey and Rubin[40] that transitional forms exist between the characteristic cells of gastric atrophy and those of gastric cancer.

Summary and Conclusions

Review of 1222 patients with the diagnosis of pernicious anemia at the Boston City Hospital, including 658 studied at the Thorndike Memorial Laboratory, confirms previous reports of the high prevalence of gastric cancer among these patients. Depending on the sample selected, however, the frequency of gastric cancer in the present series varied from less than 1 per cent to more than 11 per cent. At this hospital approximately 10 per cent of the patients with pernicious anemia had gastric cancer by the time they died or left the clinic (presumably dead).

This high rate of cancer warrants the routine use of screening tests. The relative simplicity and accuracy of gastric cytology justify consideration of its use as a screening adjunct.

Table 4. *Yearly Number of Patients with Pernicious Anemia in Whom Gastric Cancer Had Developed by 1951 (Total of 21 Patients).*

Year	Patients Known to Have Gastric Cancer in Stated Year	Other Patients in Whom Gastric Cancer Subsequently Developed*	Reservoir of Patients with Gastric Cancer†
			%
1918	—	—	—
1919	—	—	—
1920	—	—	—
1921	—	—	—
1922	—	—	—
1923	—	—	—
1924	—	—	—
1925	—	—	—
1926	—	—	—
1927	—	1	3.3
1928	—	1	2.2
1929	1	1	3.2
1930	—	3	3.0
1931	1	4	6.5
1932	1	6	7.6
1933	0	8	10.4
1934	0	9	11.2
1935	0	10	12.3
1936	0	10	10.3
1937	1	9	9.3
1938	2	10	10.4
1939	2	8	8.5
1940	2	7	8.0
1941	1	6	6.1
1942	0	8	6.6
1943	1	8	7.6
1944	0	9	7.5
1945	4	6	9.0
1946	1	5	6.7
1947	1	5	7.7
1948	0	6	9.7
1949	3	3	11.5
1950	4	1	
1951	2	?	

*By October, 1951.

†Incidence of patients seen in given year & not known to be alive in October, 1951.

We are indebted to Drs. Herbert L. Lombard, Arnold Lear, John Harris and Barbara Wiard, and Miss Geneva Daland, Miss Margaret Lawless and Miss Barbara Benson for their assistance in this study.

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THE MECHANISM OF INCREASED INTRACRANIAL PRESSURE INDUCED BY MORPHINE*

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MORPHINE produces a rise in cerebrospinal-fluid pressure[1] that is particularly dangerous in patients with pre-existing intracranial hypertension. It has been suggested that changes in pressure resulting from a variety of anesthetic drugs are secondary to their effects on pulmonary ventilation.[2,3]

The availability of nalorphine,§ an effective morphine antagonist, has allowed a new approach to the problem of the mechanism by which this increase in intracranial pressure occurs. The following work was designed to study this mechanism, and the results support the hypothesis that elevations of cerebrospinal-fluid pressure after therapeutic doses of morphine are secondary to elevation of arterial carbon dioxide tension resulting from respiratory depression.

METHOD

Nineteen unselected patients without neurologic disease who were to receive spinal anesthetics through intrathecal catheters, for a variety of surgical procedures, were the subjects for this study. A polyethylene catheter, which was inserted in the subarachnoid space, was left in place after the operation, and the measurements described below were made during the second to fifth postoperative hours. In addition to a spinal anesthetic — tetracaine (Pontocaine) — all subjects had received an intramuscular injection of a vasopressor drug before anesthesia and small amounts of thiopental intravenously during the operation. One group of seven subjects received atropine subcutaneously as the only preoperative medication. The other group of 12 subjects were given subcutaneous injections of morphine and atropine before anesthesia. The cerebrospinal-fluid pressure was measured with a water manometer connected to a catheter, and with the subject in the supine position; the reading referred to the level of the point of insertion of the catheter. Recordings were begun when the subjects were awake, though drowsy, and when the pressure had been stable for twenty minutes. In the patients who had received only atropine preoperatively 10 mg. of nalorphine was given intravenously. When the new cerebrospinal-fluid level had stabilized and at least thirty minutes had elapsed, 10 mg. of morphine was given intravenously, and a

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§Kindly supplied as Nalline by Merck and Company, Incorporated, Rahway, New Jersey.

similar thirty-minute observation period followed. In those who had received morphine before operation the experimental 10-mg. dose of morphine was given intravenously, after which the cerebrospinal-fluid pressure was observed for thirty to forty-five minutes. This was followed by an intravenous injection of 10 mg. of nalorphine and a similar observation period.

The effect of these drugs on the alveolar gas composition and ventilation was studied simultaneously with the measurements of cerebrospinal-fluid pressure in 2 subjects. Alveolar gas was collected by a continuous Rahn sampler and pumped to a Pauling oxygen tensimeter and thermal-conductivity carbon dioxide analyzer. The exhaled volume was measured by passage through a gas meter, which also recorded the respiratory rate. A dead space of 150 cc. was assumed for calculation of alveolar ventilation.

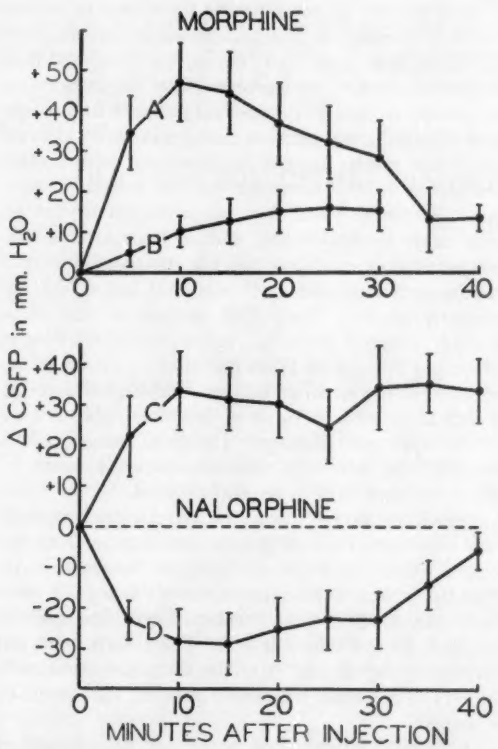

FIGURE 1. *Change in Cerebrospinal-Fluid Pressure (CSFP) after Intravenous Injection of Morphine and Nalorphine (10 Mg.).*

A=*effect of morphine alone.*

B=*effect of morphine thirty minutes after nalorphine (10 mg. intravenously).*

C=*effect of nalorphine alone.*

D=*effect of nalorphine thirty minutes after morphine (10 mg. intravenously).*

Each point is the mean value of all subjects. The vertical lines represent ± (standard error of the mean).

RESULTS

The effects of morphine and nalorphine on cerebrospinal-fluid pressure are summarized in Figure 1. The mean cerebrospinal-fluid pressure in the 17 subjects before the start of the experiment was 237 ± 11 mm. of water, which is higher than the usually accepted normal value. This elevation is attributable in part to the fact that the pressures were measured with the subjects in the supine position.[4]

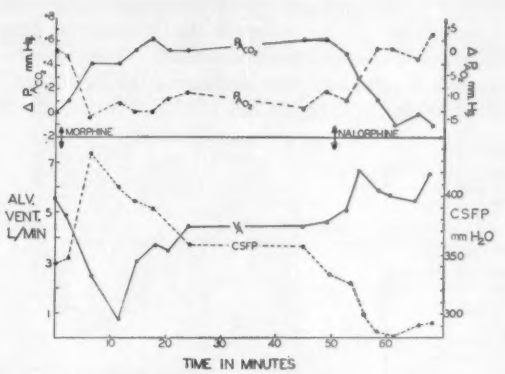

FIGURE 2. *Simultaneous Measurements of the Effect of Morphine and Nalorphine on the Cerebrospinal-Fluid Pressure (CSFP), Alveolar Gas Composition ($P_{A_{CO_2}}$ and $P_{A_{O_2}}$) and Alveolar Ventilation (V_A) in 1 Subject.*

Morphine produced the expected rise. Nalorphine had a similar effect when given initially without prior morphine medication. When morphine was given after nalorphine, a partial blocking effect and smaller rise was observed. Nalorphine given after morphine produced a marked fall in cerebrospinal-fluid pressure.

Since ventilatory depression and resultant carbon dioxide accumulation has been shown to increase intracranial pressure[5,6] simultaneous measurements of cerebrospinal-fluid pressure, alveolar ventilation and alveolar gas composition were made on 2 subjects. The experimental procedure was similar to that described for the other subjects. The results from these 2 subjects were similar; therefore, those from only 1 are presented (Fig. 2.). The parallel changes in alveolar ventilation, oxygen and carbon dioxide tensions and cerebrospinal-fluid pressure after morphine administration are apparent. The increase in cerebrospinal-fluid pressure was associated with a fall in alveolar ventilation and by an increase in alveolar carbon dioxide and a fall in alveolar oxygen composition. These changes were reversed by nalorphine. The failure of these changes to reach a steady state at the peak values is probably the result of the intravenous administration of the drugs and perhaps of secondary adjustment mechanisms.

To test the hypothesis that the rise in cerebrospinal-fluid pressure is due to respiratory depression, the

effects of hyperventilation on the changes observed after morphine and nalorphine were studied in 3 subjects. The results were similar; the data on 1 subject are presented in Figure 3. The initial fall in cerebrospinal-fluid pressure that followed hyperventilation before any drug was administered is thought to have resulted from a decreased cerebral blood flow secondary to lowered carbon dioxide tension.[5,7] Simultaneous hyperventilation and intravenous injection of morphine did not increase the pressure as long as hyperventilation was continued. When it was stopped, the pressure rose. Repeating the hyperventilation again produced a fall in the pressure, which

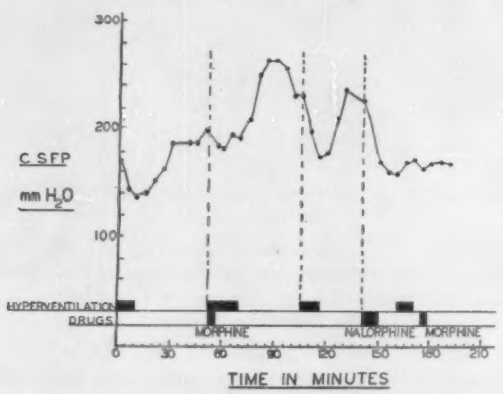

FIGURE 3. *Effect of Hyperventilation on the Cerebrospinal-Fluid Pressure (CSFP) and Its Interaction with the Effects of Morphine and Nalorphine.*

increased again when hyperventilation was stopped. The administration of nalorphine after morphine lowered the cerebrospinal-fluid pressure to approximately the level before the administration of morphine. Hyperventilation then produced insignificant changes, and the previously administered nalorphine successfully blocked the effects of subsequent administration of morphine.

DISCUSSION

Elevation of arterial carbon dioxide tension by either respiratory depression or an increase in inspired carbon dioxide concentration results in a rise in cerebrospinal-fluid pressure as a reflection of an increase in cerebral blood flow[2] and cerebrospinal-fluid production.[8]

The data presented suggest that the effects of morphine and nalorphine are attributable to this mechanism, which is invoked by the action of these drugs on pulmonary ventilation. Both morphine[9] and nalorphine[10,11] when given alone cause a decrease in alveolar ventilation. Nalorphine when given first prevents the ventilatory depressant effects of morphine in animals.[12] The antagonism of morphine-induced respiratory depression by nalorphine is well known.[10]

When morphine was given alone it consistently caused a depression of ventilation associated with a rise in cerebrospinal-fluid pressure. Nalorphine consistently caused a rise when given alone.

When nalorphine was used as a morphine antagonist, however, its effect in overcoming the ventilatory depression was associated with a fall in cerebrospinal-fluid pressure, the fall in the 2 subjects so studied occurring after the increase in pulmonary ventilation. This suggests that its antagonistic effect on the pressure was secondary to its effect on ventilation rather than that the pressure action caused the change in ventilation. This inference is further supported by the demonstration that a similar reversal of the elevation of cerebrospinal-fluid pressure produced by morphine could be achieved by voluntary hyperventilation.

These studies do not separate the effects of an elevation in alveolar carbon dioxide tension on the cerebral blood flow from its effect on cerebrospinal-fluid production. Assuming, however, that the instantaneous change in cerebrospinal-fluid pressure in our subjects reflected instantaneous changes in cerebral blood flow,[13] our results are not in agreement with certain conclusions in the literature on the action of morphine. Cerebral blood flow, as measured by the nitrous oxide method before and an hour after a subcutaneous dose of 20 to 30 mg. of morphine in 7 healthy pregnant women,[14] was said not to be significantly altered. Statistical analysis of the data, however, shows a mean rise in cerebral blood flow of 3.8 cc. per 100 gm. of brain per minute, with a standard error of the mean of 1.24 cc. This significant rise, as indicated by a P value of less than 0.05, is consistent with our findings. Its small magnitude is probably the result of the subcutaneous route by which the morphine was administered.

In another study[15] using the nitrous oxide technic data were presented as percentage change from the control values on 5 normal subjects twenty minutes after the intramuscular injection of 10 mg. of morphine. In 1 subject the cerebral blood flow rose 58 per cent; in the others it fell. The results were not statistically significant, and the data indicated wide changes in cerebral respiratory quotient that were not explained.

The evidence presented above for the efficacy of nalorphine in lowering the cerebrospinal-fluid pressure after its elevation by morphine not only has been useful in investigation of the mechanism for the intracranial-pressure effect of morphine but also suggests its trial under clinical circumstances as an antagonist to this sometimes dangerous morphine effect.

SUMMARY AND CONCLUSIONS

The effects of morphine and nalorphine on the cerebrospinal-fluid pressure of postoperative patients were studied. In 2 subjects measurement of pulmonary ventilation and alveolar gas composition were

made simultaneously with the measurements of cerebrospinal-fluid pressure. The effects of hyperventilation on the observed changes after morphine and nalorphine were also studied.

The results support the hypothesis that the increase in intracranial pressure produced by morphine is the result of an increase in arterial carbon dioxide tension, with its consequent rise in cerebral blood flow, secondary to a decrease in pulmonary ventilation.

The elevation of cerebrospinal-fluid pressure produced by morphine can be abolished by nalorphine or hyperventilation.

We are indebted to Ruth Schnakenberg for technical assistance.

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OLIGURIA FOLLOWING DIAGNOSTIC TRANSLUMBAR AORTOGRAPHY

Report of a Case

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BOSTON

TRANSLUMBAR aortography has assumed increasing importance in clinical medicine as a diagnostic aid for a variety of conditions. This technic has been of particular importance in elucidating the pathology of intra-abdominal vascular lesions,[1] and numerous reports have appeared suggesting that it is a relatively innocuous procedure with no fatal complications.[2-5] One group of authors has reported over 1000 cases without any deaths or significant morbidity.[6] It has been emphasized that patients with marginal renal function, impending gangrene of the extremities, allergy to iodine or in a poor general condition should not be considered candidates for this diagnostic procedure.[5]

Deaths after abdominal aortography are rarely described in the medical literature. One such report[7] mentions a fatal reaction to sodium iodide inadvertently injected into the superior mesenteric artery, resulting in gangrene of the bowel. This agent is no longer the radiopaque medium of choice, and fatal cases that followed the injection of iodopyracet (*U.S.P.*)¶ for abdominal aortography have not been noted by us in the literature although they most probably have occurred. The study completed in 1953 by Pendergrass et al.,[8] which was based on a survey of deaths and unfavorable reactions that followed the administration of radiopaque mediums for intravenous urography, noted approximately 1 immediate death of an anaphylactoid nature in 153,000 examinations and an even smaller figure for delayed deaths occurring later than an hour after the injection. In these reactions the contrast medium used was iodopyracet in almost every case. Although these figures have only an indirect bearing on deaths after translumbar aortography, presumably the anaphylactoid type of death would have the same frequency if the same agent were used. The complications that may arise from abdominal aortography have been defined as acute iodism, extravasation of the contrast medium, hematoma development, direct injection of secondary arterial branches, with subsequent injury to the organ supplied, and extension of an arterial thrombosis.[9] The problem of iodism has been reviewed, and the caution necessary when iodide injections are considered in the presence of renal disease has been emphasized.[10] In general, however, abdominal aortography has not been attended by any significant morbidity or mortality, and this is in marked contrast to the experience with carotid arteriography and with angiocardiography.[11-15]

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¶Available as a 70 per cent solution, Diodrast Concentrated Solution.

Because of the expanding use of this diagnostic technic and because of the paucity of reports concerning complications from translumbar abdominal aortography, the following case is presented:

Case Report

P.P.W. (M.G.H. 83 44 51), a 57-year-old married salesman, entered the hospital with the diagnosis of thrombosis of the abdominal aorta. The illness had begun 2 years previously, when he noticed a cramp in the left calf after walking 3 or 4 blocks. This symptom gradually progressed and extended into the right calf as well. Two months before admission the patient noted some difficulty in obtaining an erection, and at the time of admission he could walk only 500 feet before stopping because of bilateral hip pain. Four months previously, in another hospital, an aortogram had revealed a block in the abdominal aorta.

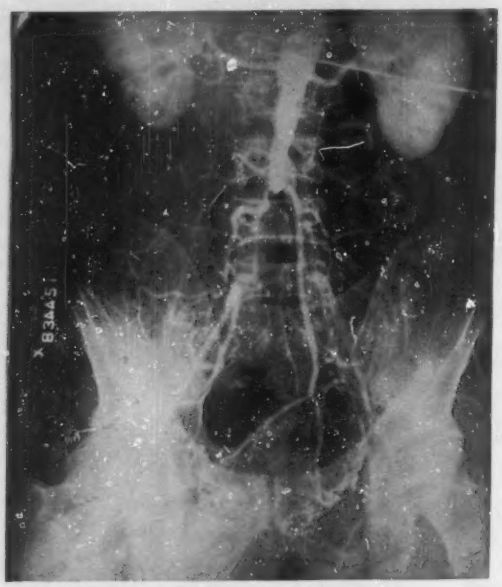

Figure 1. *Aortogram Taken after the Injection of 50 Cc. of 70 Per Cent Iodopyracet.*

The past history was not remarkable except for a coronary attack 4 years before hospitalization, after which the patient had pain radiating up to the jaws and neck bilaterally on exertion. During the few months before admission this angina of effort had subsided considerably, but on walking rapidly he noted mild substernal sensations radiating into the neck. He had no orthopnea, dyspnea, palpitation or ankle edema. Inguinal herniorrhaphies were performed 4 years and 20 years previously. A review of the systems was entirely negative except for the cardiovascular history, and there was no pre-existing renal disease, allergy or history of iodism.

The patient's father had died at the age of 64 from heart disease, and his mother at the age of 77 from undetermined causes.

The only remarkable findings on physical examination were absent femoral and distal pulsations in the lower extremities. The feet blanched on elevation and filled with blood very sluggishly in a dependent position. The heart was normal.

The blood pressure was 135/90. The pulse was 70, and the respirations 20.

Examination of the blood showed a hemoglobin of 15.5 gm. per 100 cc., and a white-cell count of 12,000 with 80 per cent neutrophils, 1 per cent large and 13 per cent small lymphocytes, 2 per cent myelocytes, 4 per cent eosinophils and a normal-appearing smear. Urinalysis demonstrated a specific gravity of 1.030, with an acid reaction, and negative tests for albumin, sugar and bile; the sediment contained occasional red and white cells, a few bacteria, and small amounts of mucin and yeast cells. The total protein was 6.8 gm. per 100 cc., with an albumin-globulin ratio of 1.8. The prothrombin time was normal. The nonprotein nitrogen was 32 mg., and the fasting blood sugar 77 mg. per 100 cc. An electrocardiogram disclosed changes consistent with coronary-artery disease and an old myocardial infarction. X-ray examination of the chest showed clear lung fields and a heart shadow of normal size and shape. The aorta appeared to be slightly tortuous in its thoracic portions.

On the 3d hospital day a translumbar abdominal aortogram was taken to determine the status of the aortic block. The needle was introduced in an anteromedial direction under the left 12th rib, and the aorta was felt to be sclerotic. Only a feeble flow of blood returned through the needle, and an initial extravasation of 20 cc. of 70 per cent iodopyracet was revealed by a trial x-ray study. After a scout film demonstrated the correct position of the needle, 50 cc. of 70 per cent iodopyracet was injected rapidly into the aorta, without any unusual reaction except for a moderate amount of transient nausea and retching occasionally seen with this procedure. The aortogram (Fig. 1) showed excellent filling of the renal, superior mesenteric and inferior mesenteric arteries. The aorta appeared to be obliterated below the 3d and 4th lumbar interspace, but the dye reached the iliac arteries by a very rich anastomotic plexus.

On the 4th day after this procedure bilateral adenitis of the submaxillary glands developed, with enlargement to twice their normal size. They appeared to be soft and nontender, and it was thought that they represented an iodine reaction to the injection of iodopyracet, to which the patient had been sensitized by the previous aortogram. On the following day the glands were smaller and firmer, but it was noted that progressive oliguria had developed since the aortogram. Physical examination at that time revealed a weight gain of approximately 8.2 kg. over the normal weight. The face appeared somewhat puffy, but there was no ankle edema. The blood pressure was 170/110. Fine, crackling rales were heard at both bases, more distinctly on the right than on the left and extending halfway up the lung fields posteriorly. Abdominal examination was negative, and there was no costovertebral-angle tenderness.

The patient was placed on a routine for acute renal insufficiency whereby his fluid intake was sharply restricted. No salts were permitted intravenously or orally. A cation-exchange resin* was given orally to promote potassium excretion in the stool, and only carbohydrates were included in the diet to provide an adequate caloric intake to decrease tissue breakdown. As the volume of urine gradually increased, the high-carbohydrate intake was enlarged by fat and by modest amounts of protein to make the diet more palatable. On the 8th day after the aortogram a loud leathery friction rub was heard over the pericardium, and 2 days later, despite the restricted fluid intake, he manifested cardiac failure and was placed in a cardiac bed and digitalized. The cardiovascular status gradually improved over a period of several days. For approximately a week he had painful, swollen left elbow and knee joints. These were thought to be either manifestations of acute gout precipitated by the renal insufficiency or another symptom of iodine allergy. Two weeks after the aortogram he became lethargic, taciturn and discouraged, and for approximately 7 days his personality was significantly changed. On the 21st day after the aortogram his mental status improved, and he was more in touch with his environment. Coincident with this favorable trend he began to eat freely, and his strength returned so that he could walk. During the final week in the hospital his disposition was quite cheerful, and the urinary output maintained a sustained volume of over 2 liters. Throughout the entire course he was afebrile except for the 1st week after the aortogram, when the temperature occasionally rose to 100°F. by mouth. Crysticillin was given on the 5th day after the aortogram through the 12th day as prophylaxis

*A sodium polystyrene sulfonate resin with a particle size of 100 microns, kindly supplied by Winthrop-Stearns, Incorporated, New York City.

against any pulmonary infection. At the time of discharge the patient was placed on a low-protein diet, and his activity was mildly restricted. He was advised to continue the digitalis.

Figure 2 presents the pertinent data extracted from the clinical record. The discontinuity in the horizontal time scale between the day of and the 5th day after the aortogram should be noted. The decline in the nonprotein nitrogen after the diuresis, the response to the resin compound seen in the decreasing potassium values, the transient hypertension and the progressive weight loss are well demonstrated.

Discussion

A few cases of parenchymal damage to the kidney after arteriography have been reported in the literature. In 1,[16] an unstated volume of sodium iodide solution was injected accidentally into the left renal artery, and this patient had severe pain in the left flank for forty-eight hours but subsequently had a normal phenolsulfonphthalein excretion from this kidney. It was thought by the authors that no permanent damage had followed this perfusion with sodium iodide. A second case report[17] states that one kidney accidentally received 30 cc. of 70 per cent Dijodon Leo during an attempt at aortography. No unusual findings were discovered on urinalysis, but there was a temporary lowering of the urea clearance; however, no permanent damage ensued. The same report[17] states that 38 patients undergoing abdominal aortography were carefully followed for urinary output, concentrating ability, nonprotein nitrogen, urea clearance and microscopical examination of the urine, no significant changes being observed. A third study[18] concerning the tolerance of the kidney to contrast mediums presents the following pertinent case report:

> Translumbar aortography was performed . . . on account of papilloma of the renal pelvis of the left kidney. The right renal artery was punctured, and a selective filling was obtained of this vessel with a pronounced nephrographic effect in the right kidney. After puncture of the aorta proximal to the origin of the renal arteries a second injection was given. Left nephrectomy 3 days later was followed by anuria with increasing N.P.N., and despite dialysis treatment, the patient died 6 weeks after aortography. The right kidney was considerably enlarged and microscopic examination showed pronounced damage, mainly of the convoluted tubules. It seems probable that the function of the right kidney had been impaired by the aortographic examination and that renal insufficiency had been masked by the good function of the left kidney. Thus, no symptoms or signs of impaired renal function were noted until after operation.

The radiopaque medium used was not stated. The disclosure of renal impairment after unilateral nephrectomy is of interest in that it demonstrates the possibility of unilateral renal damage without clinical manifestations. We have noted only 1 report[19] in which previous sensitization seems to have been involved in renal failure. In this case a patient had a normal intravenous urogram five months before a second urogram with 20 cc. of 30 per cent Joduron. During the following seven days the patient became severely oliguric, the blood urea nitrogen rising to 187 mg. per 100 cc. The patient died of acute renal failure on the seventh day, and autopsy revealed large, pale, edematous kidneys with some parenchymal hemorrhage. No evidence of previous disease was noted, and the histologic diagnosis was "chemical toxic nephrosis."

Additional emphasis must be placed on careful experimental work[18] in which the effect of iodopyracet, obtained as Umbradil, was noted on rabbit kidneys. After the perfusion of the kidneys with concentrations and amounts of the medium comparable to those employed in clinical arteriography, the renal lesions produced commonly disappeared within two or three days. Complete healing histologically was seen in a majority of the experiments although a group of rabbits with a greater exposure to the medium showed irreversible changes, with punctate areas of necrosis. Suggestive evidence was also presented indicating a rising risk of extensive injury to the kidneys with successive injections. Wide variations in the sensitivity of the animals to the Umbradil were recorded.

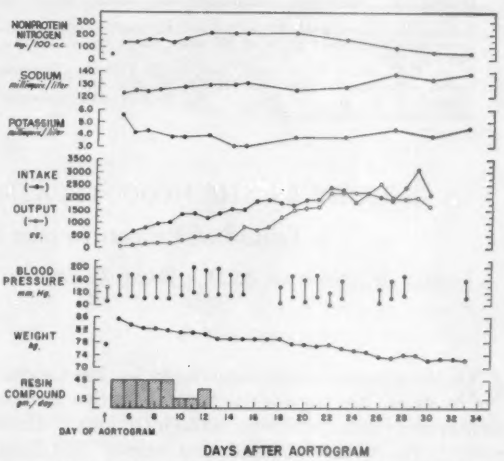

Figure 2. *Hospital Course after the Injection of Iodopyracet.*

Summary and Conclusions

A case of prolonged oliguria after diagnostic translumbar aortography, believed to be the first report concerning this complication with iodopyracet (Diodrast) is presented. A complete block of the abdominal aorta caused both kidneys to be perfused with a high concentration of the contrast medium. This may have produced renal parenchymal damage, or possibly the previous exposure to an iodinated compound resulted in an allergic reaction manifested by oliguria. Other cases of renal damage are cited from the literature. The treatment of the oliguria followed well established practice, the patient progressing gradually toward an apparently complete recovery.

The information to be gained from translumbar

aortography must fully justify the inherent risks of the procedure. These risks and their frequency will become apparent by accurate reports of the complications.

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STUDIES IN THE HOME TREATMENT OF STREPTOCOCCAL DISEASE*

I. Failure of Patients to take Penicillin by Mouth As Prescribed

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ORAL administration of penicillin has been shown by many investigators to be an effective form of treatment of appropriate bacterial infections.[1-5] However, it has been remarked that one of the disadvantages of the oral route is that a large share of the responsibility for carrying out the prescribed therapy rests with the patient.[6-8] This may lead to a failure to complete the full course of treatment and may thereby significantly influence effective control and prevention of disease. It appears from the studies done by the Streptococcal Disease Laboratory in Cheyenne, Wyoming, and from other investigations that rheumatic fever can be prevented if the preceding infection with the beta-hemolytic streptococcus is treated adequately with penicillin and the organism completely eradicated.[6-11] Since oral administration of penicillin must be continued for seven to ten days to eradicate the organism in streptococcal pharyngitis, it is of paramount importance that the patients take the drug for this period.[1,5,9,12]

For these reasons a study was undertaken to determine the completeness with which penicillin by mouth was taken by patients treated in their homes.

Methods

A total of 245 patients with acute pharyngitis or otitis media due to the beta-hemolytic streptococcus treated by the Home Medical Service of the Massachusetts Memorial Hospitals were included in this study, which was carried out during the period from July, 1954, to January, 1955. These patients were treated by supervised Boston University medical students, who spend a month on the Home Medical Service during their senior year. All patients lived in a low-income area of Boston regularly served by the Home Medical Service. Of the total number of patients 217 were fifteen years of age or less and 23 were over fifteen. A routine schedule of 200,000 units of potassium penicillin G tablets three times a day by mouth for seven days (total of 4,200,000 units) was prescribed.

All patients, or the responsible adult in cases involving children, were interviewed at home by one of us after the conclusion of the course of treatment. When the prescribed amount had not been taken, further inquiries regarding the reason were made. The questions were presented in a manner intended to encourage truthful answers.

Results

Of the 245 patients questioned 161, or 65.7 per cent, stated that they took oral penicillin for seven days as prescribed. Eighty-four, or 34.3 per cent, admitted taking less than the prescribed amount (Table 1).

After the first three months of the study it was obvious that a large number of patients were not taking the prescribed amount of penicillin. At this time the medical students were not aware that the study was in progress. It was therefore decided to discuss with all subsequent students the results of the first three months, to emphasize their role in explaining to patients the need for following the

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prescribed course of treatment and to determine the effects of such an explanation on the performance of the patients.

Table 2 shows that 60.1 per cent took the penicillin as directed before emphasis was employed and 70.9 per cent took the penicillin as directed after emphasis. Although this represented a desirable trend the increase was not statistically significant.

Of the 84 patients who failed to take the full amount of penicillin, 56 per cent took the drug less than five days, 25 per cent took it for five or six days, and 19 per cent took it for six or seven days. In this group the average number of days for which the drug was taken was four (Table 3).

When the group was divided into patients fifteen years of age and younger (88.1 per cent) and patients older than fifteen (11.9 per cent), it was found that 67.7 per cent of the children took the drug as prescribed whereas only 50 per cent of the adults did so. Parents appear to be more conscientious about their children's health than about their own. However, the number of adults was small, and the difference between the two groups was not statistically significant (Table 4).

Table 5 lists the various reasons given for not taking the full amount of penicillin. The most frequent was that the patient felt well after one or two days of therapy and thought that continuation of the drug was accordingly unnecessary (36.9 per cent). The next most common reason was related to the first in that once the patient began to feel well, he became careless in following the prescribed course (27.4 per cent). Other reasons were insufficient money to buy the full number of tablets prescribed (16.6 per cent), refusal of young children to take the tablets, which included vomiting of the tablets (10.7 per cent),* and a misunderstanding of the doctor's instruction (8.4 per cent).

Eighty, or 32.7 per cent, of the total were receiving financial assistance from the Department of Public Welfare. These patients, who received medications without charge, did not differ in performance from the rest of the group.

TABLE 1. *Patient Performance.*

PERFORMANCE	NO. OF PATIENTS	PERCENTAGE
Pencillin as prescribed	161	65.7
Less penicillin than prescribed	84	34.3
Totals	245	100.0

TABLE 2. *Patient Performance before and after Emphasis.*

PERFORMANCE	NO. OF PATIENTS	PERCENTAGE
Before emphasis:		
Penicillin as prescribed	71	60.1
Less penicillin than prescribed	47	39.9
Totals	118	100.0
After emphasis:		
Penicillin as prescribed	90	70.9
Less penicillin than prescribed	37	29.1
Totals	127	100.0

*Penicillin by mouth was not prescribed in cases complicated by serious nausea and vomiting.

TABLE 3. *Number of Days Penicillin Was Taken by Those Who Failed to Take the Prescribed Amount.*

NO. OF DAYS TAKEN*	NO. OF PATIENTS	PERCENTAGE
6 - 7	16	19
5 - 6	21	25
<5	47	56
Totals	84	100

*Average, 4 days.

DISCUSSION

It is apparent from these results that a significant number (34.3 per cent) of the patients admitted taking less than the prescribed course of penicillin by mouth and accordingly received inadequate therapy. The true number of such failures may actually have been greater because, despite the care taken in phrasing questions, certain patients may have given an incorrect answer to "please" the questioner. The clinical and bacteriologic outcome of these patients will be reported in a subsequent study now in progress.

TABLE 4. *Comparison of Performance in Older and Younger Age Groups.*

PERFORMANCE	NO. OF PATIENTS	PERCENTAGE
Patients 0-15 yr. old:		
Penicillin as prescribed	147	67.7
Less penicillin than prescribed	70	32.3
Totals	217(88.1%)	100.0
Patients over 15 yr. old:		
Penicillin as prescribed	14	50.0
Less penicillin than prescribed	14	50.0
Totals	28(11.9%)	100.0

TABLE 5. *Reasons for Not Taking Penicillin As Prescribed.*

REASON	NO. OF PATIENTS	PERCENTAGE
Patient felt well	31	36.9
Carelessness	23	27.4
Insufficient money	14	16.6
Refused tablets	9	10.7
Misunderstanding	7	8.4
Totals	84	100.0

These findings are particularly significant to clinics and physicians treating a large number of strepto-

coccal infections with penicillin. It is suggested that the degree of unreliability encountered in the routine oral use of penicillin constitutes a significant disadvantage in obtaining effective therapy. In hospitals, where the taking of the medication is supervised by nurses, this is not a problem.

Also, in the daily prophylactic oral use of penicillin and sulfadiazine in patients with rheumatic fever the same problem arises. It has been found at the Good Samaritan Hospital in Boston that when streptococcal infections appear while prophylactic penicillin is being taken by mouth, they usually occur in patients classified as unco-operative.[13]

Summary

Of 245 patients treated in their homes with a seven-day course of penicillin by mouth, 34.3 per cent admitted not taking the prescribed course of penicillin.

Of the patients who failed to take the prescribed amount, 56 per cent took the drug for less than five days, with an average of four days.

The most frequent reason for not taking the drug properly was that the patient felt well after one or two days of therapy. Other reasons were carelessness, insufficient money, refusal of children to take the drug and a misunderstanding on the part of the patient.

Patients receiving medication without charge through public assistance did not differ in their performance from the rest of the group.

It is believed that this constitutes a serious problem in the oral use of penicillin for the effective treatment of the ambulatory patient with streptococcal infection and in the prophylaxis of rheumatic fever.

We are indebted to Henry J. Bakst, M.D., professor of preventive medicine, Boston University School of Medicine, and to Mindel C. Sheps, M.D., M.P.H., lecturer in biostatistics, Boston University School of Medicine, for their assistance in the preparation of this paper.

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SPECIAL ARTICLE

BOSTON MEDICAL LIBRARY

Report of the Librarian*

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BOSTON

THE Librarian herewith presents his annual report, the seventeenth accounting of the state of the Library since he took office in 1938. The report covers the calendar year 1954, another year of increased attendance, indicating an upward trend of usefulness in the period since the end of World War II. The circulation figure was slightly less than in 1953, but above the previous three years. The volumes at the end of 1954 numbered 224,477, and the catalogued pamphlets, 158,481. The accessions in books were 2,165, and those in pamphlets 1,896. The periodicals and serials currently received were 1,042. In general these figures indicate that the Library grew in 1954 at about its predicted rate, with an addition of slightly over 4000 items.

*Presented at the annual meeting of the Boston Medical Library, April 6, 1955.

As usual, many books and journals came to the Library as gifts, and we are particularly indebted to the American Optical Company, the Lahey Clinic, the *Journal of Bone and Joint Surgery* and the *New England Journal of Medicine* for their contributions. Gifts too came from the Boston hospitals, the Harvard Medical School Library, the Armed Forces Medical Library, the John Hancock Life Insurance Company, Arthur D. Little Company and others. Special gifts were received from Drs. Marshall L. Alling of Lowell, William H. Bartlett, John H. Cunningham, John G. Kuhns, Oliver A. Lothrop, William J. Mixter, L. F. Playse, of Georgetown, Maine, and Fritz B. Talbot. Mrs. Leary gave us the library of the late Dr. Timothy Leary, Mrs. O'Connor the library of Dr. Alfred S. O'Connor, of Worcester, and Mrs. Sproull the library of Dr. John Sproull, of Haverhill. A particularly

valuable accession was autographed copies of books by Sir William Osler received from Dr. Joseph H. Pratt and another group of Osler books from Mrs. Henry Chapin, Lady Osler's sister. Other gifts came from the American Antiquarian Society of Worcester, the Marine Biological Library, the E. L. Patch Company, the University of Maine, the Worcester Hahnemann Hospital and the Christian Science Publishing Society. Of special interest also were the books and pictures used by the late Walter L. Burrage in compiling his history of the Massachusetts Medical Society, a gift from his son, Dr. Walter S. Burrage. Mrs. Frank A. Hayden, of Andover, presented an eighteenth-century bleeding knife, and Dr. E. J. Holmyard, of London, a long run of the scientific and popular journal, *Endeavour,* containing frequent articles of medical interest.

Many accessions were purchased with special funds designated for specific purposes. The principal items are briefly noted below, along with some discussion of their relative importance.

Accessions

Incunabula and Early Manuscripts

One manuscript and only one book and an almanac printed before 1500 were added to our historical collection, but each was an important accession. The total number of such items in the Library is now over 800. The manuscript, in Persian script, Miftáh-ul-Khazá'in, or "Key to the Treasures," by Alí bin Husayn al-Ansárí (1329-1403), is a pharmacopoeia, giving examples of simple drugs, their rectification and a final chapter on compound preparations. The author, the son of a physician, was one of the greatest pharmacists of the Mongol period. He lived in Shiraz and was personal physician to the Sháh, the patron of Háfiz, the Persian poet, with whom al-Ansárí must have been well acquainted. The original work was written about 1366. The Bodleian Library at Oxford has two copies of this book, one in the handwriting of al-Ansárí, the author, dated 1367. Written in Naskh characters on Samarkand paper, the present copy was completed in 863 A. H. (1458 A. D.). It contains prescriptions of Avicenna (980-1037), the Arabian physician and the greatest name in medicine from 1100 to 1500. The Library has a number of manuscripts of the *Canon* of Avicenna, written in Arabic, Hebrew and Latin, but none in Persian, although one of the finest of the Arabic manuscripts was written in Persia about 1309 (Ballard, *Catalogue,* 8).

To the commentaries on Aristotle by Thomas Aquinas the Library added the second incunabula edition of *De Physica,* probably printed in Venice by Nicolus Jensen, in 1480 (Stillwell T.224), the Library having no other edition of this book and no copy of any of the three editions published before 1500 being recorded in New England.

The *Almanach auf das Jahr 1494* is a particularly well preserved example of a German broadside, probably published in Nürnberg by Kaspar Hochfeder in 1493. The text is complete, and the edges uncut, a condition rarely found in this type of fifteenth-century printing since most of the yearly almanacs were discarded after the year of issue or used up and disfigured. Bookbinders, moreover, used them to line the sides and back of bindings, so that many were torn when subsequently removed, usually across the middle section, which lay against the back strip. The edges, often cut to fit a binding, are frequently defective. The Library has 22 examples of almanacs published before 1500, some showing the defects noted above. It appears as though the 1494 almanac, although somewhat wormed, had never been used as part of a binding, but had been preserved intact.

Of the almanacs acquired since 1944, some are among the finest examples in the whole collection. A brief description follows:

1471. This is next to the oldest, being exceeded only by the fragment of 1470 by the same printer. It is a bleeding calendar, finely printed in German in black, and carries the name of Guntherus Zainer von Reutlingen, Augsburg, in the colophon. The top and right margins have been cut, with the loss of a few letters, but otherwise the almanac is complete, except for a few insignificant worm holes. Parts have been restored, with the text of a few words added in facsimile. Zainer's first printing dates from 1468; he died in 1478. The Library has three other almanacs printed by Zainer, for the years 1470, 1476 and 1477, and two books, published in 1472 and in 1473.

1481. This is a dated almanac, printed in Augsburg by Johann Blaubirer. It is complete, with a decorative, woodcut border of the letter *"I"* on the left margin and a word-scroll as a New Year greeting at the top. A two-column table in German gives the phases of the moon, followed by the text on the most favorable days for blood letting, printed entirely in black. There are a few defects in the paper affecting one or two words. Blaubirer printed books from 1478 to 1486. The Library has no other example of his work, but he is known to have printed another calendar for 1481 and one for 1483.

1485. This is a complete almanac, with wide margins, cut in two parts but not affecting text, printed in Latin by Johann Petri, as was an almanac, previously acquired, for the year 1487. The latter is more elaborate, with a large woodcut initial and scroll top, with motto. The 1485 copy carries a smaller initial. Both are printed in black and are of similar design, but the 1485 is the finer copy. Petri printed from 1485 to 1493 in Passau, Bavaria.

1487. This complete, blood-letting almanac, in German, was printed in red and black, by George Reyser, of Würzburg. The center is defective, for

the sheet was used as a part of a binding of a book, and the middle section, used for the backstrip, was torn on removal. The moon phases are given, and the critical days, calculated for Nürnberg, are indicated. There are two woodcuts of the moon. This is the only example of the printing of Georg Reyser in our incunabula collection. Reyser began printing in 1479 and continued after 1500.

1492. This is a dated almanac, in Latin, printed in red and black by Martin Landsberg, of Leipzig. It is a bleeding calendar, in the usual form, calculated for Leipzig. The right margin has been shaved, and part of the woodcut border at the bottom is missing. The text is otherwise complete. The calculations were made by Faber von Budweis, of Wenzel, who was also the author of the almanac for 1496 and of a table for the conjunction of the sun and moon, published in Leipzig, 1494. The Library has, in addition, a number of books printed by Landsberg before 1500.

1494. This is one of the finest of the almanacs, complete, with wide margins, printed in Nürnberg, by Kaspar Hochfeder. It is a bleeding calendar, dated, in German, printed in red and black, with woodcut borders at top and left edge, a fine initial and three phases of the moon. The paper is somewhat wormed, but the text is readable. The Library also owns an elaborate almanac for the same year, also printed by Kaspar Hochfeder, in Latin, showing the eclipses, calculated by Jacobus Honiger, for various cities.

1498. This almanac, in German, was printed by Johann Zainer, in Ulm, and compiled by Hans Virdung, of Hassfurt, who also compiled the almanac of 1492. At the top is an elaborate woodcut of Venus riding on a fish, and there is a decorated left border, with a representation of Adam and Eve. The back is signed by "Nicolaus Ellenbog 1499." The sheet has been cut in half, possibly without loss of text, but the right-border woodcut is partly missing, and the lower edge cut into. The text is all in black. The signature is that of Nicolaus Ellenbog, the son of Ulrich. He was born in 1481 at Biberach, where his father was in practice, and he studied in Memmingen and Heidelberg. In 1499, when he signed the almanac, he was eighteen; a student home from Heidelberg, where he was in 1497 and presumably adopting and carrying on his father's scholarly pursuits, for his father died in the same year. Nicolaus became prior of the monastery of Ottobeuern in 1504, and there his books and those of his father rested until the nineteenth century, when they were sold. Some came to rest in the Cushing Library at Yale, and others in the Boston Medical Library. One of the almanacs (for 1485) was signed by Ulrich Ellenbog in 1488. Ulrich, the father, was born in 1430 and also studied at Heidelberg. He obtained his medical degree at Pavia in 1459. His son was not a doctor of medicine.

The twenty-two almanacs, although relatively small in number compared with all that were printed, give a picture of medicine as it was practiced in Bavaria during the last half of the fifteenth century — Bavaria because, of the eight cities where the broadsides were published, only one was outside that state in southwest Germany. The exception was the almanac issued at Leipzig in Saxony. Seven almanacs originated in Augsburg, and six in Nürnberg, and the others were scattered from Ulm to Passau. Augsburg, on the Lech, with its clear mountain water and the center of the cloth industry, must have been a good place for a printer, and some of the earliest printing was done there by Günther Zainer, Johann Schüssler, Anton Sorg and Johann Blaubirer. It was here too that Ulrich Ellenbog, the doctor, took part in the setting up of an important press at the Monastery of SS. Ulrich and Afra in collaboration with Abbot Melchior von Stamhaim in the last months of 1473.

In Nürnberg, Anton Koberger had begun printing in about 1471, and Friedrich Creussner as early as 1472. Kaspar Hochfeder did not come until twenty years later, in 1491, but Johann Müller, better known as Regiomontanus, was one of the pioneers in Nürnberg, probably as early as 1471. His mathematical knowledge and scholarly attainments in the collation of Greek manuscripts must have made him a welcome addition to the Nürnberg group, and he was soon busy setting up his observatory and his press. He was shortly, however, called away to Rome to revise the calendar and did not return to Nürnberg after 1475. Not long afterward, Peter Henlein was working on his portable watches, the "Nürnberg eggs," so large at first that they had to be hung from the girdle, and Albrecht Dürer, the goldsmith's son, born in Nürnberg in 1471, was apprenticed to Michael Wolgemut and, by 1494 had established his own studio. The old medieval town must have been a pleasant place to live in during the last quarter of the fifteenth century, but plague was an ever-present menace, as witnessed by the fifteenth-century *Pestblatt* printed in Nürnberg and other Bavarian cities.

The almanacs, moreover, cover sixteen of the years between 1470 and 1500, although in six of them there are two for single years. All but one of these were issued from different cities. The years represented are 1470, 1471, 1472, 1476, 1477, 1478, 1481, 1482, 1484, 1485, 1487, 1492, 1494, 1496, 1498 and 1499 (Table 1).

Astrologic medicine. Medical almanacs may be considered an essential guide to the practice of medicine, particularly in relation to bleeding and purgation, two forms of treatment greatly favored by fifteenth-century physicians. They were frequently issued each year for this primary purpose. Some, extending over a period of years, were called calendars, but the terms were often used interchangeably, as in the German form of *Laxier-kalender* or *Aderlass-kalender,* even when only one year was given. The

text sometimes went beyond the notation of "favorable days" for bleeding or purgation, including the treatment of wounds, bonesetting, amputations, with added folk literature on anniversaries, home medical advice, statistics, jokes and even fiction and poetry. This all led naturally to the almanacs of Nathaniel Ames and Benjamin Franklin, in the eighteenth century. By that time, however, most of the serious import of astrology had disappeared. The situation was far different in the fifteenth century. Criticism and even legal action might well follow if phlebotomy was carried out on an unfavorable, or "Egyptian," day. Even in 1437, long before the first printed purgation (1457) or blood-letting (1462) almanacs, the University of Paris was called upon to settle a controversy on "favorable days" for these operations. Before the days of printing, the manuscript almanacs were marked with a cross for favorable days and with a half-cross for those reasonably certain not to produce disaster. The appointed university arbitrators compromised on the value of specific days, but both thought that every physician or surgeon should possess a comprehensive almanac to tell what sign the moon was in every day and with what planets, good or evil, it was related.

Venesection, purging and drugging in general had long been regulated by the age of the moon and Bede, the seventh-century English historian, wrote a treatise on phlebotomy based on astronomic data. April 8 to May 25 were all lucky days; during the rest of the year all days when the moon was full were "Egyptian," and any form of treatment at such a time was not advised. By the eleventh century, when the Church forbade monks to wear beards, barbering became a trade and from the first barbers it was only a short step to minor surgery, such as bleeding, cupping, leeching, the giving of clysters or extracting teeth. Thus the barber surgeons were among the first to need medical almanacs, and when the Army field surgeon treated wounds, set bones or amputated, he too needed his astrologic computations. But the grim realities of war and the urgency of operation soon turned the best of the barbers, like Pfolspeundt, Brunschwig and Gersdorff, toward realities and away from astrology, thus leading up to the Renaissance in medicine, as developed by Paracelsus, Vesalius and Paré. Medical almanacs slowly disappeared, but not until the twentieth century. With them went bleeding and violent purgation as major forms of treatment for general disease, but astrology is retained in some places and consultations with the stars and planets before major decisions are not unknown. To Ellenbog and his brother practitioners, however, surgery on "Egyptian" days was almost unthinkable.

Sixteenth-Century Books

The Library has long endeavored to collect the works of the Lyon physician, humanist, encyclopedist and teacher, Symphorien Champier. He will be remembered partly for his influence on Miguel Servet and other contemporary physicians. In the *Report of the Librarian for 1952*, the Library's holdings of twenty books, in twenty-six editions, by Champier,

TABLE 1. *Fifteenth-Century Printed Almanacs in Boston Medical Library.*

YEAR	PLACE	PRINTER	LANGUAGE	BALLARD CATALOGUE NO.	
Added before 1944:					
1470	Augsburg	Günther Zainer	German	98	
1472	Augsburg	Johann Schüssler	German	99	
1476	Augsburg	Günther Zainer	Latin	100	
1477	Augsburg	Günther Zainer	German	101	
1478	Nürnberg	Friedrich Creussner	German	102	
1481	Nürnberg	Printer of Rochuslegende	Latin	103	
1482	Nürnberg	Printer of Rochuslegende	Latin	103	
1484	Bamberg	Johann Sensenschmidt	German	114	(Johannes Angeli)
1485	Augsburg	Anton Sorg	German	104	
1487	Passau	Johann Petri	German	105	
1492	Leipzig	Konrad Kachelofen	Latin	711	(Johannes Virdung)
1494	Nürnberg	Kaspar Hochfeder	Latin	378	(Jacobus Honiger)
1496	Nürnberg	Kaspar Hochfeder	German	106	
1496	Ingolstadt	Johann Kachelofen	German	309	(Faber von Budweis)
1499	Bamberg	Johann Pfeyl	German	107	
Added since 1944:					
1471	Augsburg	Günther Zainer	German	G.W. 1288/20	
1481	Augsburg	Johann Blaubirer	German	G.W. 1346	
1485	Passau	Johann Petri	Latin	G.W. 1394	
1487	Würzburg	Georg Reyser	German	G.W. 1420	
1492	Leipzig	Martin Landsberg	Latin	G.W. 9554	(Faber von Budweis)
1494	Nürnberg	Kaspar Hochfeder	German	G.W. 1491	
1498	Ulm	Johann Zainer	German	G.W. (Einbl.) 1491	(Hans Virdung)

with one other book attributed to him, were listed. In 1954 the Library acquired one of the most desirable of Champier's publications (Fig. 1): *Le questionaire des Cirurgiens et Barbiers. Auec le Formulaire du petit Guydon en cirurgie veu et corrige et: les Lunettes des Cirurgiens de nouveau adjoustez. Et Imprimez nouvellement a Paris.* (Paris: Pierre Sergeant, 1533). Through the kindness of Professor William A. Jackson, of the Houghton Library, it was learned that this copy was formerly owned by Monsieur J. Renard, of Lyon, and sold with his books in Paris in 1881. It is listed as 313 in the *Catalogue de*

livres rares et précieux . . . de la Bibliothèque de M. J. Renard (de Lyon) (Paris, 1881), but the date of the book is given erroneously in the catalogue as 1538, instead of 1533. It was formerly owned by J. L. A. Coste, of Lyon, who is cited by Brunet, and was tightly bound by the well known firm of Koehler. The volume carries the bookplate of J. Renard.

The book is in three parts. The first contains the questions and answers used by examiners at the

Le questionai-
re des Cirurgiens et Barbiers/ Auec le
formulaire du petit Guydon en cirurgie Deu
ment corrigez: et les Lunettes des Cirurgiens de
nouueau adioustez/ Et Imprimez nouuel
lement a Paris.
Dy les vend a Paris en la Rue neufue
nostre dame a lenseigne sainct Nicolas.

FIGURE 1. Le questionaire des Cirurgiens et Barbiers *(Paris, 1533)*.

medical school at Montpellier. This part is unsigned and undated. A large section is given over to the treatment of wounds by cautery, and there are illustrations of these instruments. The work was translated into English by George Baker as *Guydos Questions, newly corrected* (London: Thomas East, 1579), and is known as "Guydo his Questionaries." It may be assumed that Gui de Chauliac was the author and that the questions and answers are those used by him at Montpellier in the fourteenth century.

The second part contains *Le formulaire des aydes des apostemes et pustusses ordonne a paris par maistre guidon de caillac cyrurgien et maistre en medecine a montpellier en lan mille trois cens quarante.* It carries the imprint of *Pierre Sergeant demourant en la rue neufue nostre Dame a lenseigne sainct Nicolas. En lan mil cinq cens xxxiii.* The author, of course, was Gui de Chauliac, but the name of the person who made the abridgment is not given.

The third part, published over Champier's name, is *Le myrouel des Appothicaires et pharmacopoles,* a digest of medicines suggested by Hippocrates, Galen and other ancient writers. The last part contains *Les lunettes des Cyrurgiens Francoys.*

The first part contains 64 leaves, the second 24, and the third 44, making 132 leaves, or 264 pages. The gatherings are as follows: A-H^8; A-C^8; and A-E^{8}F^4. It is possible that the parts were also sold separately, but in this copy the title page carries all three parts.

The book, published in Paris near the schools of medicine, was certainly designed for the student. Written in French, it must have had an appeal to the less learned of the student population, poorly versed in Latin. The first part indicates the comprehensive type of examination given at Montpellier, the leading medical school of the time, particularly in anatomy and wound surgery. The influence of the great Gui de Chauliac, held over from the fourteenth century, and Galenism, astrology and meddling surgery were still dominant in France but not entirely in Italy. The second part, taken directly from Gui de Chauliac, is only one of the many abridgments made by Champier and others. The great surgery of Gui was printed in Lyons as early as 1478, but these little guides, the "petit guydon," were the most popular form of medical literature and hardly any surgeon or barber would be found without one in his saddle bag. Since the name "Guy" and the word "guide" stem from the same root, the terms became synonymous, as for one who leads the way and directs, or carries the pennant or guidon. The "guidon" was, in one aspect of surgery, an unfortunate influence, for Gui accepted the teachings of Roger and Roland on the needs for suppuration of wounds before healing could be accomplished. Poultices and salves were extensively used to bring this about. If he had taken the word of Bruno and Theodoric that desiccation with wine and closure by sutures was the correct procedure, in anticipation of Listerism, the whole course of surgery would have been favorably advanced a number of hundred years. Champier, by his translation into the vernacular, only made this erroneous method more popular, but the primary fault lay with Gui, who could not adopt the "fables" of Theodoric, although the evidence lay directly in front of him.

The third part, *Le myrouel des Appothicaires et pharmacopoles,* is a critical digest of medicines suggested by Hippocrates, Galen and other ancients and is followed by the *Lunettes des Cyrurgiens et Barbiers.* Both are composed by Champier. Potton, whose excellent account of Champier, with an analysis of his works, is little known *(Ann. Soc. de méd. de Lyon* 11:328-381, 1863), finds in *Le Myrouel* an attempt on the part of the author to reinforce his

ideas against Arabic medicine by writing in French, using as a basis his previously published books in Latin. *Les Lunettes,* or spyglass for French surgeons, is a condensation of the principles of surgery, largely based on Gui de Chauliac, but covering the whole history of surgery.

The Library also added a fine copy of the third edition of *Tractatus Perutilis et Completus de Fractura Cranei* (Venice, 1535), by Berengario da Carpi, fully described in *Berengario da Carpi* by Vittorio Putti, a comprehensive monograph published in Bologna in 1937, which contains an Italian translation of the first edition of 1518. An account of Putti, the orthopedic surgeon, and his famous library at the Istituto Rizzoli will be found in the *New England Journal of Medicine* for December 5, 1940 *De Fractura* is not a rare book in Italy, but only two other copies are recorded by Putti in America and another in the Osler Library in Montreal. The book contains, besides the picturesque illustration on the title page (Fig. 2), figures showing the trephine, with various types of drills and other surgical instruments used in craniotomy, not dissimilar to those in use today. The binding is a good example of contemporary tooled leather.

Berengario, the friend of Cellini, a surgeon of note, an artist and a scholar, taught at Pavia and Bologna, but he is usually associated with Ferrara, where he died in 1530 at the age of sixty. A renowned anatomist, he did dissections, making drawings of the parts to serve as illustrations for his books. But his practice in both medicine and surgery was extensive, and he left a large fortune. In medicine he is credited with the introduction of mercury in the treatment of syphilis, and in surgery he once excised the uterus for prolapse, a formidable operation in the sixteenth century, without anesthesia, asepsis or a sound knowledge of the control of bleeding. He is said to have treated wounds conservatively. The book on cranial injury was little known until Putti called attention to its importance.

Another important accession was *Macri de materia medica,* edited by Janus Cornarius (Frankfort, 1540). This herbal in verse, usually referred to as *Macer floridus,* is attributed to Odo of Meudon, a French physician, who probably wrote *De viribus herbarum* contained in the first three of the five parts of the book. The verse was popular in the Middle Ages, and the Library has a fine fourteenth-century manuscript in Latin (Ballard 35) and also the first printed text, published at Geneva, some time before 1500 (Ballard 443). The style may stem back to Aemilius Macer, a Roman didactic poet, who in turn imitated Nicander, the Greek poet. The most famous English edition is *Macer's Herbal practysyd by Doctor Lynacro* (London, 1530?), also in the Library. Even Thomas Linacre apparently found it worth while to translate this book from Latin into English for his less learned colleagues, but the book, badly printed, is only a rough, abbreviated excerpt of the poem. If the "Doctor Lynacro" on the title page is really the same man, not much credit can be given to the learned classical scholar for so poor a book. J. N. Johnson, the biographer of Linacre, believes that Robert Wyer, the printer, surreptitiously employed Linacre's name to the translation of Macer. Cornarius was an early editor of Hippocrates's works.

FIGURE 2. De fractura cranei, *by Berengario da Carpi (Venice, 1535).*

Other sixteenth-century books acquired were as follows: Raymond Lull, *Ars Magna generalis et ultima* (Lyon, 1517); Hieronymus Cardanus, *Cl. Ptolemaei . . . de astrorum judiciis* (Lyon, 1555) and *Geniturarum exemplar* (Lyon, 1555).

English Imprints

Albertus Magnus. *The secrets of Albertus Magnus. Of the vertues of herbes, stones, and certaine beasts.* (London: T. Cotes, 1637) (S. T. C. 267). Although the Library has many editions of Albertus in Latin, this is the first acquired in English. This great naturalist of the thirteenth century was a Dominican monk and thus was forbidden to write specifically on medical practice, but in his descriptions of herbs there are many medical implications. Much of the

book is filled with astrology, old wives' tales and divinations. *The Secrets* contains little of value and gives a poor picture of a great teacher whose influence was very wide. The book was brought to the Library by Dr. Douglas Guthrie, of Edinburgh, on his visit in 1954 and was purchased from him to add to our collection.

Pharmacopoea Londinensis (London: Edward Griffin, 1618) (S. T. C. 16,772). This was the first official pharmacopoea of the College of Physicians

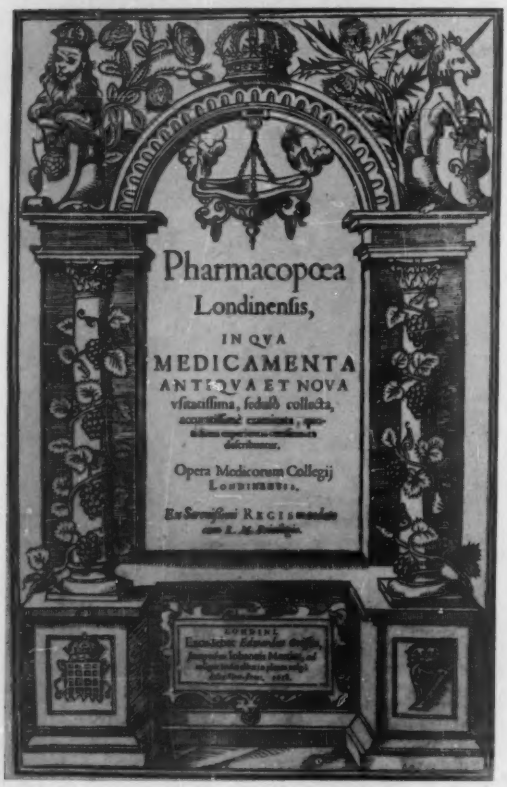

FIGURE 3. Pharmacopoea Londinensis *(London, 1618).*

(Fig. 3), commanded by King James, which all apothecaries were to follow. It was compiled under the direction of a committee, headed by Henry Atkins, the president, and Theodore de Mayerne, the King's physician, and including Mathew Lister, William Harvey, Robert Fludd and others. The book contained all the filthy medicines in use in the seventeenth century — worms, vipers, foxes' lungs, oil of ants and moss from the skull of a victim of violent death. It was not until Sydenham's time, later in the century, that many of the worst ingredients were omitted from practice, although retained in this official publication up to Heberden's attack in 1745. The book was translated into English by the herbalist and quack, Nicholas Culpeper.

Enchiridion Medicum: containing, an epitome of the whole course of physicke: with the examination of a chirurgion . . . and an antidotary . . . published for the benefit of young students in physicke, chirurgions, and apothecaries (London: Henry Ballard for George Potter, 1609). This is not in S. T. C., but 24577 appears to be the same book, issued in 1608. It is attributed to Petrus Pomarius Valentinus, a pseudonym. The first part is "An epitome of the whole course of physicke" in the doctor-and-student questionnaire form, similar to *Guydos Questions.* The second part, "The examination of a chirurgion . . . by way of a dialogue betweene the doctor and the student," by S. H., contains the famous passage, "I would to God that this citie of London were altogether furnished with such Chirurgions; then should there not be so many ignorant and unskillful suffred to abuse so noble an art, and withall the Kings liege people; in taking upon them the profession of that wherein they have no knowledge at all: but I leave that to them that have authority to amend it." The Library has also the enlarged, second edition of this book, printed in 1612 and the gift of Dr. John T. Bottomley some years ago.

Johann Jacob Wecker. *A compendious chyrurgerie: gathered, & translated (especially) out of Wecker . . . by John Banester* (London: John Windet, 1585) (S.T.C. 25185[a]). Wecker was a Basel physician who had written an *Antidotarium* in 1574 and in 1576 and a *Practica* in 1585. John Banester, the anatomist and surgeon, is best remembered by his well known portrait, depicting him as giving a lecture at the Barber Surgeons' Hall in London in 1581. He had obtained his Oxford degree in 1573 and went to London from Nottingham at Queen Elizabeth's request. His works were collected in a fine quarto edition, published in London in 1633, including the book noted above. This collection is also in the Library.

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Pasqual, Antonio-Raymundo. *Vindiciae Lullinae, sive demonstratio critica immunitatis doctrinae . . . Raymundi Lulli . . .* 4 vol. (Avignon, 1778).

A transcript of the registers of the Company of Stationers of London, 1554-1640. 4 vol. (London, 1875-1877); *Index* (Birmingham, 1894). Ed. by Edward Arber. Reprinted (New York, 1950).

A transcript of the registers of the Worshipful Company of Stationers from 1640-1708. 3 vol. (London, 1913-1914). Reprinted (New York, 1950).

Enciclopedia universal illustrada Europeo-Americana. 70 vol. *Appendices.* 10 vol. *Supplemento.* 6 vol. (Madrid, 1934-1944). This comprehensive work contains biographies and notes of many physicians not found in other encyclopedias.

Library Notes

Exhibitions

The following exhibitions were held: plant books, herbals from Dioscorides to Brunschwig; for the Jewish Tercentenary, books by Jewish authors, early books in Hebrew from 1200 to 1500 A.D. and books by modern authors, with pictures of physicians and portraits; for an exhibit at the Wadsworth Athenaeum, Hartford, we sent ten items, covering the years 1483 to 1816, with American, English and German imprints.

Publications

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Idem. Pest and syphilis. *New Eng. J. Med.* **250**: 491, 1954.

Idem. Myasthenia gravis. *New Eng. J. Med.* **251**: 97-105 and 141-145, 1954.

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MEDICAL PROGRESS

ORAL MEDICINE (Concluded)

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Pigmentation

Normally, one finds the oral cavity free from natural melanin pigment except in dark-complexioned Caucasians and dark-skinned races. When present, pigmentation is noted principally on the gums and the buccal mucosa and lips. Eliminating normal findings, the presence of melanin pigment in the oral cavity may suggest some constitutional disease in the body and may give the first clue to such a condition. Oral melanin pigmentation may be associated with intestinal polyposis as described by Jeghers et al.[26] We have noted 4 such cases over a period of twenty years and undoubtedly overlooked others before articles on this rare syndrome began to appear in the literature. The syndrome consists of two features: distinctive melanin spots of the buccal mucosa and lips and intestinal polyposis. The face and the digits may be involved to a variable extent, but the mouth pigmentation is the *sine qua non* of this portion of the syndrome. The stomach, colon and rectum may be involved, but the presence of polyps in the small intestine is a constant feature of this portion of the syndrome. Sufficient genealogic data are reported to demonstrate the hereditary nature of the syndrome, which appears to be inherited as a simple mendelian dominant.

Considerable investigative work in the mechanism of melanin production has been published in recent years.[27] Melanin is formed in melanocytes, which are cells derived embryologically from the neurocrest and located in skin and mucous membrane. It has been shown that tyrosinase, an enzyme occurring in the cytoplasm of melanocytes, catalyzes the oxidation of the amino acid tyrosine to melanin. Many factors, such as the concentration of tyrosine and tyrosinase, the presence of inhibitors and temperature, are involved in melanin formation. Recently, more insight into the endocrine control of pigmentation has been reached,[28] helping one to understand the increase of oral melanin pigmentation in Addison's disease and occasionally in pregnancy, as well as after the use of ACTH. Normally, pigmentation is controlled by several hormonal factors. The pituitary gland releases the melanocyte-stimulating hormone, which produces increased pigmentation. Hydrocortisone from the adrenal cortex inhibits the release of this hormone. In Addison's disease decreased adrenocortical function lowers the production of hydrocortisone. This provokes a compensatory increase in ACTH and melanocyte-stimulating hormone. If the adrenal medulla is also destroyed, epinephrine production, which is an inhibitor of the hormone, is reduced. Thus, the melanocytes become dark by the increased action of the stimulating hormone. The increased heat present in the mucous membranes of the oral cavity further accentuates the tendency to production of melanin pigment. The accelerated pituitary activity during pregnancy accounts for the pigmentary increase often observed in gravid women's

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skin although the mucous membranes are rarely affected. When ACTH is given, there is an accompanying increase in melanocyte-stimulating hormone.

Bismuth pigmentation of the oral mucosa, associated with the therapeutic administration of bismuth preparations in the treatment of syphilis, is now a rare finding. The occasional use of bismuth is confined to a few dermatologic conditions. Clinical and pathological findings in a large number of cases were reported by one of us (F.P.M.) in 1936.[29] The pigmentation was located chiefly on the gingival margin and occurred microscopically in the tunica propria, found as amorphous granules of bismuth sulfate in endothelial and phagocytic cells. Gingival calculi represent the important causative irritative factor in deposits of the bismuth granules.

TABLE 1. *Psychosomatic Factors in Skin and Mouth Conditions.*

LESION OR SYMPTOM	NO. OF CASES
Cancerphobia (more often related to tongue)	216
Papillitis	211
Oral lichen planus	97
Habit biting	27
Ptyalism	15
Cheilitis exfoliativa (6 out of 40 cases)	6
Syphilophobia	2
Total	574

Extraneous pigmentation is rarely observed by accidental impregnation of the oral mucosa, usually involving the gingivae by amalgam particles. Orban[30] has reported these discolorations, which are chiefly amalgam and which result from fragmentation during the extraction. The amalgam fragments may lodge in the wound and remain in the socket after healing. When the remnants are located superficially, the mucous membrane covering them shows a deep-bluish discoloration. Radiopaque particles can also be seen in these areas on the roentgenogram. Traumatic or implantation cysts may contain amalgam particles due to injury by amalgam plugging.

PSYCHOSOMATISM

Psychosomatic factors have assumed an important place in both skin and mouth conditions. In our recent survey of oral diseases we were impressed by the fact that a great number of patients seen in both office and clinic were classified in this group. In our study approximately 11 per cent of all the cases seen were related to psychic causes. Lesions and symptoms related to the tongue comprised the largest number in this group (Table 1).

In our series of 4728 cases[24] we classified as cancerphobia only cases of the more pronounced types, since practically all the female patients beyond middle life with oral lesions or symptoms expressed some fear of cancer. In extreme cases dissipation of fears in these patients represents a real problem, and only after repeated visits is it possible to overcome the phobia.

Patients with syphilophobia are now rarely seen by the stomatologist, undoubtedly because it is known that the disease is under control as a result of antibiotic therapy.

Papillitis, involving the fungiform papillae at the dorsum of the tongue, usually near the tip, is the commonest psychosomatic condition we have seen, and in a high percentage of cases it is related to self-inflicted irritation occurring in neurotic persons. One may see these patients rubbing their tongues usually against the lower central and lateral incisors, where tartar tends to accumulate to excess, leaving a rough, irritating surface. It is often necessary to use magnification to demonstrate the swollen and reddened papillae, usually seen at the tip of the tongue. In marked cases a burning sensation of the tongue is kept active by the frictional activity of the tongue that the patient produces in seeking relief from the burning sensation.

Habit biting usually causes maceration of the buccal mucosa, occurring both unilaterally and bilaterally. This type of lesion may on cursory examination suggest leukoplakia, but one may readily peel off the macerated epithelium in establishing the diagnosis.

Lichen planus involving the oral cavity occurs in about 50 per cent of all cases of this disease. In our series of nearly 100 cases involving the oral cavity, we lean strongly to the psychosomatic factors as the cause of this entity. There is considerable difference of opinion about the etiology, and many dermatologists do not accept lichen planus as a psychosomatic disease.

The same underlying psychogenic factors that are found in dermatologic disorders are present in the psychosomatic mouth conditions. Sulzberger and Zaidens[31] have described the psychogenic causes in a variety of skin conditions, including neurotic excoriations, pruritus ani, vulvae and scroti, neurodermatitis and other less common skin diseases.

Most observers seem to agree that emotional disturbances with various tensions and impulses have a definite influence on these psychosomatic oral and skin conditions. There is real disagreement about the relative importance of these factors, particularly in individual cases. We have been able to get but limited help from the psychiatrists, and whatever help we can offer is given with our routine treatment such as patient listening, with explanation, local application, sedation, various physical modalities and ultra-violet, Grenz-ray and x-ray therapy.

DRUG ERUPTION

The enormous numbers of new drugs introduced in the past few years have been associated with a corresponding increase in adverse reactions. Although almost every organ and tissue may be involved, the

oral mucous membranes have felt the full impact of these reactions. Many of the clinical pictures are based on an allergic phenomenon. However, other mechanisms may be in force such as idiosyncrasies, intolerance, primary irritability and more obscure disturbances. The widespread enthusiasm for local application of medicine in the form of troches, lozenges, toothpaste and chewing gum has also helped produce undesirable side effects. Careful questioning concerning drug exposure has become an indispensable part of the history of all stomatologic examinations, and many physicians and dentists have developed a high degree of suspicion concerning drug reactions. Extensive and persistent questioning along these lines often discloses the causal agent for numerous reactions in the oral cavity. Rephrasing of questions often brings to light medications that the patient considered unimportant. Continued interrogation on subsequent visits also uncovers considerable information. Since the subject is too great to be considered in its entirety, we shall restrict discussion to reactions seen with antibiotics and to the therapy of drug reactions in general.

Antibiotics

There are numerous reports in the literature on the oral complications of antibiotics. A tremendous variety of reactions has been observed, ranging from a mild evanescent erythema to severe necrotizing and generalized eruptions that have proved fatal. Reactions to both the local and systemic use of these drugs have been reported. Certainly, there is nothing specific about drug reactions. They may mimic many types of disease and symptom complexes. At one time syphilis was known as the "great imitator." Perhaps adverse drug reactions now deserve that title with the great diminution in the prevalence of syphilis. The possibility of sensitization to this group of drugs has been well established. We have seen a considerable group of patients with mild to severe involvement of the oral cavity. The most severe and dangerous is the vesiculobullous variety, which may give the picture of erythema multiforme bullosum. The so-called Stevens–Johnson syndrome may be the result of sensitivity to an antibiotic. The vesiculobullous stage is very fleeting, owing to the fragility of the walls of these lesions, and early rupture leaves painful erosions. This was the group that could be confused with pemphigus before the newer histologic studies. In our experience penicillin has been a chief offender for this type of stomatologic picture. The broad-spectrum antibiotics have brought with them newer and more complicated problems. It is true that straight allergic reactions from these drugs occur, but they are less common than the controversial and confusing clinical picture that has been attributed to a vitamin deficiency on one hand and a disturbance of the normal flora of micro-organisms on the other.

Many of the patients present a diffuse erythema or beefy-appearing tongue, with marked erythema of any or all of the remaining mucous membrane. Angular cheilitis is often present, and dryness and burning sensations are common, along with various taste disturbances. There is no doubt, however, that various members of the vitamin B complex are synthesized by the action of bacteria that constitute the normal intestinal flora. The broad-spectrum antibiotics can suppress many of these organisms and thus interfere with the normal production of vitamin B complex. Some observers[32] believe that the administration of components of the vitamin B complex along with the antibiotics will reduce the frequency of reactions and that they are also a useful form of therapy once the unfavorable reaction has taken place. One pharmaceutical house is now marketing a wide-spectrum antibiotic incorporated with vitamins. We have not been particularly impressed with results of vitamin B therapy and believe that, although it may be a factor, other mechanisms are involved.

There is more definite evidence[33-36] that the altering of the bacterial and mycotic flora may produce various oral reactions. There is no doubt that the antibiotics bring about a change in the normal flora. The only question that exists is whether the clinical picture is due to the floral alterations. Many dire predictions have been made about the eventual serious systemic fungous infections that would result from the use of antibiotics, but to date the evidence is very meager. Most systemic cases of moniliasis have been observed in patients greatly debilitated by leukemia, other malignant processes and serious chronic diseases. Even the less serious local complications, such as thrush and possibly lingua nigra, are not common and again are almost exclusively found in patients suffering from a severe chronic disease.

One point that we wish to emphasize is that the mere finding of candida organisms does not constitute a diagnosis of moniliasis unless typical clinical signs of that disease are also present. The presence of the organisms must be considered a coincidental finding in the absence of clinical evidence of moniliasis. Furthermore, Robinson[37] was unable to culture *Candida albicans* more frequently after antibiotic therapy than before the institution of these drugs. There has been considerable excellent clinical and experimental work on this problem.[38-40] It appears to substantiate the position that antibiotics may upset the flora of micro-organisms of the oral cavity and the gastrointestinal tract. However, unless the person is susceptible because of lowered resistance and the drugs are continued for prolonged periods, significant side effects from this mechanism are few. Furthermore, within a few days of the cessation of therapy, the oral mucous membrane usually returns to normal. Although we certainly do not encourage the indiscriminate use of antibiotics many physicians are unnecessarily concerned about the production of yeast infections.

Therapy

Of course, the first step in any drug reaction is to eliminate the medicine once the undesired side reaction is observed, if this can be done without jeopardizing the welfare of the patient. In certain infections in which a specific antibiotic is life saving, most side reactions have to be ignored. However, if the drug eruption is severe enough, it may be fatal in itself, and good judgment must be exercised. When the antihistamines were first introduced, they were welcomed as the solution to all allergic reactions, but it soon became apparent that their value was limited almost entirely to the urticarial type of reaction. The only other benefit appears to be as a consequence to their soporific effect on patients with pruritus and pain. Recently, new enthusiasm has been revived regarding the intramuscular and intravenous administration of these drugs. Some have advocated mixing the antihistamines and antibiotics in the same syringe, and others report and recommend intramuscular or intravenous injection once the allergic reaction has been recognized. The experience with the use of these methods of administration of the antihistamine is still limited, and more careful and controlled studies are necessary before any definite conclusions can be reached.

The use of ACTH and cortisone has been the one revolutionary advance in the management of allergic drug eruptions. We have found that an early high dose, followed by a gradual prolonged withdrawal, has been most effective. Inadequate initial doses or hasty withdrawal may further complicate the clinical picture by upsetting the immunologic reactions to such a degree that the drug eruptions may be unnecessarily prolonged. One must remember that there is nothing curative in the action of these hormones, which merely alter the patient's reaction while the drug is present in the tissues. There is a great temptation to stop the steroids quickly upon the initial relief of symptoms, either to avoid possible complications or to spare the patient the expense of the medication. Careful, gradual reduction in dose will prevent sudden severe exacerbations and should also eliminate the danger of any complications from the steroid. ACTH and cortisone are not to be used indiscriminately on all allergic drug-induced stomatitides, many of which are mild and evanescent and can be conservatively treated by soothing bland therapy. However, when the eruption is severe and incapacitating, much pain, inconvenience and time can be spared by the judicious use of these drugs.

Systemic and Vitamin-Deficiency Diseases

Changes in the tongue may be diagnostic in many systemic diseases other than nutritional disorders. The tongue may indicate the degree of jaundice, cyanosis and pallor, with hemorrhagic lesions, pigmentation and the characteristic appearance of other changes indicative of disease elsewhere in the body. Neurologic factors may influence taste and produce tremor and paralysis, indicating a central-nervous-system disease. Atrophy of the papillae, producing a smooth or bald tongue, often reflects various types of anemia. These forms of papillary atrophy are reversible in contrast to the atrophic syphilitic glossitis related to arterial obliteration.

Vitamin A Deficiency

Only in animals, as the result of a diet deficient in vitamin A, can one demonstrate oral mucosal changes such as hyperplasia of the gums and gingivitis.[41] There is no clinical evidence that oral-mucous-membrane lesions in human beings are based on vitamin A deficiency. Vitamin B deficiency in oral disease is usually associated with a deficiency of more than one of the complex group. Among the changes attributed to deficiency of components of the vitamin B complex are gingivitis, glossitis, glossodynia, cheilosis and inflammatory processes involving the entire mucosa. Vitamin B_1 (thiamine deficiency) is not considered an important factor in the production of oral disease. Weisberger[42] described an eruption consisting of minute vesicles simulating herpes simplex, involving the palate and the undersurface of the tongue that responded to daily oral or parenteral administration of 30 mg. of thiamine. Atrophy of the tongue has also been reported.

Riboflavin deficiency, or ariboflavinosis, may be considered an important, although relatively rare, type of vitamin deficiency in its severe form, capable of characteristic signs in the oral cavity and elsewhere. Glossitis, cheilosis, seborrheal dermatitis and a superficial vascularizing keratitis are among the prominent findings. The tongue lesions vary in the mild cases from the smooth, shiny surfaces of the tongue with enlarged fungiform papillae to more severe lesions. Joliffe et al.[43] first described a characteristic glossitis attributable to deficiency of riboflavin. The tongue is clean, purplish red to magenta in color and frequently associated with fissures. The combination of riboflavin and nicotinic acid deficiency, producing essentially the same picture, requires administration of the whole Vitamin B complex for a favorable response.

Pseudoariboflavinosis

An excellent article[44] brings out the frequency of angular cheilitis in persons over forty years of age wearing old, poorly fitting dentures. Thiamine therapy fails to improve the inflammatory lesions at the external commissure. By lengthening the vertical dimension either by rebasing the dentures or replacing the old dentures with new ones, the authors brought about a prompt disappearance of these lesions in practically every case. We share the belief that so-called pseudoariboflavinosis occurs far more commonly than true ariboflavinosis, and expensive vitamin preparations should be used only after the

mechanical factors involved and poorly fitting dentures have been corrected.

Nicotinic acid deficiency, or aniacinosis, results in pellagra, which produces lesions on the tongue and gums and the oral mucosa as a whole. In the acute cases of nicotinic acid deficiency, usually associated with alcoholism, in this part of the country, the lesions consist of a bright-red tongue and prominent hyperemic, fungiform papillae, often with bullous lesions that rapidly rupture, leaving a superficial eroded area. A whitish pseudomembrane forms over these eroded areas, and when this exudate is peeled off bleeding surfaces resembling the lesions of thrush (moniliasis) are left. In chronic aniacinosis the tongue is smooth, atrophied and glazed, often with fissures and marginal serration. The rapid response to nicotinic acid therapy is noted in the acute forms.

It has been our experience that in the New England area recognizable lesions of avitaminosis in the oral cavity or lips are extremely rare, although subclinical cases of aniacinosis may occur. One can expect mucous-membrane lesions only in severe cases.

Miscellaneous Considerations

Pregnancy Gingivitis

Pregnancy gingivitis, often with associated granulomatous epulides, has attracted some attention in recent years with a marked contradiction in the reported frequency of both conditions. Granulomatous lesions usually involve the gingivae, with a tendency to inflammation of the vascular margin. The study of pregnancy gingivitis by Ziskin and Nesse[45] stresses various degrees of gingival reaction, including so-called "pregnancy tumor." An explanation based on estrogenic activity with other factors is not conclusive. In a series of 416 pregnant women the following gingival changes were observed: pregnancy gingivitis, 37.9 per cent; hypertrophic gingivitis, 7.0 per cent; raspberry-red gums, 40 per cent; and a combination of gingival changes, 1.8 per cent. In a series of 530 pregnant women Maier and Orban[46] report the following gingival findings: no pathologic change, 44.6 per cent; mild inflammation, 35.9 per cent; moderate inflammation, 17.5 per cent; severe inflammation, 1.5 per cent; and tumor formation, 0.5 per cent. These authors[46] believe that there is no significant difference in the prevalence of gingivitis in pregnant and nonpregnant women. Discrete, tumorlike gingival enlargement of pregnancy—the so-called "pregnancy tumor"—is not a neoplasm. This lesion is granulomatous and soft, bleeds freely on slight trauma and is related to local irritating factors. It usually appears after the third month of pregnancy, in which a rate of 1.8 to 5.0 per cent is reported.[46] There is spontaneous reduction in the size of the lesion, frequently with complete disappearance after the termination of pregnancy, and it is usually necessary to remove all forms of local irritation. It is our observation that pregnancy gingivitis and the so-called "pregnancy tumor" have been overemphasized, and the elimination of all sources of local irritation will minimize the likelihood of gingival enlargement in pregnancy.

Syphilis

Formerly, the manifestations of syphilitic infection in the oral cavity produced the common and readily diagnosable group of lesions but have now practically disappeared with the rarity of this disease as seen today. The manifestations of tertiary syphilis, particularly as they are related to the tongue, remain. These cases are found in older persons who contracted syphilis in their youth and who were untreated or inadequately treated, with the characteristic smooth, atrophic tongue, referred to as syphilitic glossitis. We have suggested the following explanation for the genesis and development of this pathognomonic lesion of syphilis. In the secondary stage of the disease there is a heavy dosage of *Treponema pallidum* since the tongue is a mobile organ subject to trauma. There is also a primary endarteritis, followed by a slowly developing fibrosis, with associated narrowing of the lumens of the lingual arterial blood vessels. The overlying papillae undergo atrophy, which results in a smooth, shiny surface to the tongue. This is an irreversible condition despite antisyphilitic therapy. This type of tongue is apt to develop malignancy, having lost its protective surface layer of papillae. As a result of the use of tobacco and other irritants, leukoplakia develops, and continued irritation may ultimately produce an epidermoid carcinoma, which may in some cases be multiple on the dorsal surface of the tongue. Since, at one time, up to a third of tongue cancers were secondary to syphilitic atrophic glossitis[25] and since syphilis is no longer a menace, a great reduction in this precancerous type of glossitis can be expected.

Therapeutics

There is a constant quest for new therapeutic agents, especially for diseases in which present methods of therapy are inadequate. One has only to pick up the daily mail to obtain some idea of the flood of new drugs that are pouring out of pharmaceutical laboratories. Some of these, especially from the more reputable companies, have been thoroughly tested and found to be safe as well as of definite value. Many, however, are being foisted off on the practitioner with extravagant claims based on slim evidence of effectiveness. The grasping by many physicians and dentists for any therapeutic straw has encouraged the drug houses to keep up the steady output. It may take years of experience and many negative reports to neutralize the effects of one article in the medical literature praising a new worthless drug. In the field of oral medicine there is very little of significance to report in new therapy.

Steroid Drugs

These drugs have had a tremendous influence on all aspects of medicine, and the field of stomatology is no exception. Of course, like most new "miracle drugs," they have been abused on occasion, but their definite value has greatly overshadowed the side effects. One must know their actions and limitations before launching on indiscriminate use of ACTH and cortisone because they are not cure-alls. They must be used in adequate doses and withdrawn slowly. Maintenance doses are required in some chronic diseases. It is not our purpose to discuss all the aspects of these drugs, for there are many excellent articles covering this subject. In our experience they have been most useful in the following diseases: acute allergic drug reactions, both from focal and from systemically administered drug; collagen disease such as lupus erythematosus and dermatomyositis; bullous diseases like pemphigus vulgaris, benign mucous-membrane pemphigus, erythema multiforme, bullosum and other rare conditions such as bullous lichen planus; and severe aphthous stomatitis.

Local use. We have not had success with the local use of hydrocortisone ointments in the oral cavity. Perhaps the difficulty in maintaining the drug at the desired site for any significant length of time is the main obstacle to effective therapy. However, there are no side reactions from the topical use, which may be carried on for long periods without fear of systemic manifestations.

Treatment of Fungous Disease

Recent developments in antimycotic[47,48] therapy have stimulated considerable interest in these medications. Perhaps with the alleged increase in recent yeast infection after antibiotic therapy, the whole field has become more important. Fungous disease of the oral cavity, excluding moniliasis, is not common. However, when it has occurred, therapy has been very unsatisfactory. In the past few years considerable interest has developed with the use of stilbamidine in deep mycosis. Because of the toxicity of stilbamidine a less toxic drug, 2-hydroxystilbamidine, was developed. From the reports to date[49-53] there seems no doubt that these drugs are excellent therapeutic measures against blastomycosis, histoplasmosis and perhaps coccidioidomycosis and sporotrichosis. The newer agents developed for use in moniliasis have not been as spectacular, although quite promising.

One such agent, mycostatin, has been marketed, but its effectiveness is limited to the lower portion of the gastrointestinal tract. It certainly appears probable that further great strides in the control of fungous disease in the oral cavity will be made in the near future.

Antimalarial Drugs in Chronic Discoid Lupus Erythematosus

The treatment of discoid lupus erythematosus was, until recently, very unsatisfactory. Perhaps 5 to 15 per cent of these patients presented oral lesions that were as recalcitrant as their cutaneous counterpart. Recent reports[54,55] on the effectiveness of quinacrine therapy in the treatment of this disease have been encouraging. However, the chief drawbacks have been the yellow discoloration of the skin and toxic reactions after prolonged administration. More recent studies[56,57] with another antimalarial agent with less toxicity have been reported. We have been extremely satisfied in our experience with chloroquine in the treatment of chronic discoid lupus erythematosus of the oral cavity and skin. Most cases have cleared completely although a small maintenance dose is usually necessary to prolong the clinical response. We have not encountered any side reactions other than mild nausea. The initial dose is usually 500 mg. daily for two or three weeks, followed by a maintenance dose of 250 mg. a day.

Occasionally, therapy may be adjusted according to the clinical picture; in some patients remission of the disease is prolonged after therapy is discontinued. Certainly, there is no doubt in our minds that these drugs have been the greatest single therapeutic agent in the treatment of this disease.

Tuberculosis of the Oral Cavity

Tuberculosis of the oral cavity is an extremely rare condition. Even in patients whose oral mucous membrane is almost constantly being bathed by sputum, teeming with tubercle bacilli, only a very occasional patient with greatly lowered resistance manifests oral lesions of tuberculosis. These lesions usually occur as ulcerations of the tongue, buccal mucous membrane or gingiva. The severe necrotizing tuberculosis cutis orificialis is another form of oral tuberculosis in the debilitated patient with active pulmonary disease. This condition is marked by an extremely necrotizing type of eruption about the oral cavity and extending onto the mucocutaneous junction, as well as involving the vestibule of the mouth. Primary tuberculosis is even more rare, and follows the classic primary complex as would be expected in other organs. It starts initially with what is called the "tuberculous chancre," followed by regional lymphadenopathy and gradual subsidence according to the patient's natural resistance to the disease. The introduction of streptomycin ushered in a new era in the management of tuberculosis,[58] especially the nonfibrous variety. Newer agents have subsequently been forthcoming such as iso-nicotinic acid hydrazide, and para amino salicylic acid. Reports[59] on the response of oral tuberculosis to these drugs have been encouraging. They may be used singly or in various

combinations. The marked vascularity of oral mucous membranes readily delivers a high concentration of the therapeutic agent to the diseased tissue, and a lack of fibrotic activity allows good circulation, which is often lacking in the pulmonary lesion. Thus, tuberculosis joins the ever-increasing list of diseases for which new therapeutic measures have proved effective.

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MEDICAL INTELLIGENCE

CHOLELITHIASIS IN IDENTICAL TWINS

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A SURVEY of the literature concerning cholelithiasis reveals no agreement on the probable etiology of this common disease. Several authors have postulated a congenital familial factor that predisposes to this condition, and a familial occurrence has been reported on several occasions.[1-4]

I have been able to find only one reference to cholelithiasis occurring in identical twins. Tesler,[4] in 1946, reported apparent cholelithiasis in female, identical twins aged nineteen, 1 of which was proved by operation; the other had a typical history, and x-ray study showed "a poorly functioning gallbladder with radiolucent shadows suggestive of calculi."

As further evidence of a genetic constitutional factor in the etiology of cholelithiasis, the occurrence of cholesterosis with cholelithiasis and choledocholithiasis proved by operation in identical twins aged seventeen, with a history of a similar condition in the mother, is reported.

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Case Report

These twins were born September 8, 1936, after an entirely normal pregnancy. The obstetrician in charge believed that they were definitely monovular twins.

Twin No. 1 had the usual childhood diseases, no serious medical illnesses, operations or injuries, and no symptoms of gall-bladder disease until after her marriage in 1953. During an otherwise normal pregnancy some fatty intolerance and right-upper-quadrant pain developed. She was delivered of a normal female infant on March 8, 1954. Subsequently, she had several attacks of apparent biliary colic. Cholecystograms demonstrated multiple small, nonopaque stones in the gall bladder. She was admitted to the hospital on July 11. Routine laboratory studies were within normal limits, the hemoglobin being 13.2 gm. per 100 cc., and the hematocrit 41 vol. per cent. Operation on July 13 showed the gall bladder to be full of small, soft, yellow stones; the common duct was dilated and contained 4 stones, 2 or 3 mm. in diameter. The liver, spleen, kidneys and upper gastrointestinal tract were grossly normal. The pathological diagnosis was chronic cholecystitis, with cholelithiasis, choledocholithiasis and early cholesterosis of the gall bladder. The postopera-

tive course was uneventful, and the patient is now doing well.

Twin No. 2 had the usual childhood diseases, with no serious medical illnesses, operations or injuries, except for pneumonia on 2 occasions in early childhood. At about the age of 12 she began to complain of some indigestion and discomfort after eating fatty foods. She was married in 1953 and soon became pregnant, being delivered of a normal daughter on June 30, 1954. Because of the findings in Twin No. 1 x-ray examination was carried out on August 13, a cholecystogram showing a group of small, nonopaque stones in the gall bladder. Operation was advised but was refused because she had had no severe pain or biliary colic and was having only mild symptoms. On September 13 the 1st attack of real biliary colic occurred, and 2 weeks later, after the 2d attack, she was admitted to the hospital. Routine laboratory studies were negative; the hemoglobin was 12.5 gm. per 100 cc., and the hematocrit 40 vol. per cent. At operation on October 1 the gall bladder was found to contain multiple small, yellow cholesterol stones. The common duct was normal in size, shape and position, but exploration disclosed 3 small stones, 2 or 3 mm. in diameter. The liver, spleen, kidneys and upper gastrointestinal tract were grossly normal. The pathological diagnosis was chronic cholecystitis, with cholelithiasis and cholesterosis of the gall bladder. This twin also did well postoperatively.

The mother gave a history of symptoms of chronic cholecystitis developing in 1944, when she was 36 years of age; in 1946 the gall bladder was removed by another surgeon. Pathological examination showed about 60 small cholesterol stones, with cholesterosis of the gall bladder.

Summary

A case of apparently identical twins, both of whom at the age of seventeen had multiple cholesterol stones in the gall bladder and in the common duct, with cholesterosis of the gall bladder, is reported. The mother also had had multiple cholesterol stones with cholesterosis of the gall bladder. These cases are presented as further evidence of a genetic constitutional factor in the causation of gallstones.

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BY THE LONDON POST

Army Medicine—Medical Use of Hypnotism—Candy and Caries

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LONDON, ENGLAND

THIS year the Army is celebrating the centenary of the formation of the Army Pathology Service. It was in 1855, when the sick and wounded troops in the Crimea were suffering greatly, that Florence Nightingale took the law into her own hands and introduced women nurses into the hospital at Scutari. At the same time the Secretary for War issued an instruction to a certain Irish physician, Dr. Lyons, "to make pathological researches in the hospitals attached to the Army in the East." He had two assistants assigned to him, and one of them, Dr. William Aitken (later Sir William), became the first professor of pathology in the Army Medical School. The school was opened at Fort Pitt in 1860 and moved to Netley, near Southampton, three years later. Sir William Aitken, who held the post for thirty-two years, was responsible for encouraging the development of the Army Medical Corps, the Royal prefix being granted by Queen Victoria in 1898.

It was during this time that the importance of conserving manpower in war by the prevention of disease and by proper treatment of the sick and wounded was fully appreciated. The research carried out at Netley greatly influenced the course of tropical preventive medicine. After Aitken's death Dr. Almroth (later Sir Almroth) Wright was appointed his successor at Netley. His researches there, together with those of Sir William Leishman, led to the discovery of the antityphoid vaccine, of the cause and means of prevention of Malta fever and of the isolation of the parasite of kala-azar.

During World War I there were for the first time mobile pathology units in the forward areas carrying out investigations into such little-understood forms of disease as trench feet, spirochetal fever and gas gangrene.

In 1919 Sir William Leishman was appointed the first director of the newly formed Pathology Directorate. Research continued between the wars, one of the most important results being the development of tetanus prophylaxis. The active immunization of soldiers was doubtless responsible for the remarkable lowering of the rate of tetanus from 1.47 per 1000 British soldiers engaged in World War I to the rate of 0.11 per 1000 in the campaign in North West Europe in 1944-45. During World War II the Army Pathology Service had tremendous opportunities. Research teams studied shock, typhus, infective hepatitis, diphtheria and many other diseases. Much information was also obtained about nutritional anemia and the effects of malnutrition. The wartime study of penicillin in all its aspects virtually formed the basis of modern antibiotic therapy.

And so, after one hundred years, the Army Medical and Pathological services look out upon an uncertain future. It is to be hoped that the nuclear weapons presenting the current research problems at the Royal Army Medical College will never be used. Nevertheless, in retrospect, it cannot be denied that the stimulus that wartime necessities gave to research probably brought considerable medical benefits to mankind.

* * *

Hypnotism in one form or the other has been practiced as a means of healing since early times. It was used by the ancient civilizations, usually in a religious setting. More recently, Mesmer (1734-

1815) claimed that he could cure by touching, and in fact he practiced therapeutic hypnosis. At first his treatment consisted in the application of magnets until he found he could achieve similar results by the use of hands. Hypnotism has also been of great importance to the growth of modern psychotherapy. Indeed, it was the method used by Freud to explore the depths of the unconscious mind until he evolved his system of psychoanalysis. Unfortunately, the practice of hypnotism has often been carried on by imitators, who have mostly been untrained in medicine and have often been unscrupulous. Thus, there has been a certain taint of unrespectability about the practice of the art.

The seal of respectability, however, has been conferred on this ancient art in a report of a subcommittee of the Psychological Medicine Group of the British Medical Association. The report recalls that two committees previously investigated the medical use of hypnotism, one set up by the French Royal Academy of Science in 1826 and one by the British Medical Association in 1892. The French committee recommended that magnetism as a therapeutic method should be admitted within the sphere of the medical science and as such should be practiced only by physicians. The committee of the British Medical Association believed that hypnotism is frequently effective in relieving pain, inducing sleep and alleviating functional ailments. The present committee is satisfied that hypnotism has a definite, if small, place in orthodox medicine.

All medical students should therefore be instructed in the possibilities, limitations and dangers of hypnotism as a form of therapy. Anesthetists and obstetricians in training should receive special instruction since it is of particular value in their fields. The committee has emphasized certain definite dangers, especially when hypnotism is used on persons predisposed to psychoneurotic reactions. For this reason, there is need for further research into the phenomena involved in hypnotism, and the committee has urged the organization of such research by university departments and benevolent foundations.

* * *

There is good news for children in the recently published Medical Research Council report on the relation between excess dietary sugar and caries of the teeth.

Three groups of children in London, Liverpool and Sheffield were studied for periods of up to two years. The state of their teeth was recorded at the beginning of the test and at intervals afterward. All the children were taking a good basic diet, with a liberal allowance of milk and fresh fruit. Half of them were given an average of 1 pound a week of additional sugar, and the others were watched as controls. In spite of the increased sugar intake by half the children there was no significant acceleration in dental decay in these cases as compared with the controls.

Although this observation does not prove that unlimited carbohydrate is harmless, it fails to support the idea that carbohydrate foods taken in excess are a main cause of caries in children over a short period. Because of this the children are delighted. At last, they can produce scientific evidence when objecting to parental restraint on their candy consumption. Sophisticated foods, as these starch containers have been labeled, have apparently been cleared of the time-honored charge of being at least partly responsible for bad teeth in children. It seems sad that so many generations of children have been denied unrationed sophistication. Perhaps when they were caught with sticky fingers after raiding the larder for jam and syrup, they suffered more than they deserved.

Nevertheless, the pediatric rejoicing is not shared by the dentists, who are concerned at the publicity that the report has received and fear that parents may misinterpret the conclusions of the experiment. This was, in fact, an isolated experiment, and the results were not entirely consistent with those reported by earlier workers. In a large-scale study of dental caries in Sweden, sugar was given in the form of sticky toffees between meals. In these cases dental caries was much more widespread. A spokesman of the British Dental Association therefore issued a warning. He emphasized the fact that the whole of the experiment concerned sugar added to the ordinary diet and eaten at ordinary mealtimes. It did not deal with the consumption of sugar between meals, nor with the eating of sweets. He therefore reiterated the warning that indiscriminate sucking of candy and eating of sweet biscuits are bad for children's teeth.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41261

PRESENTATION OF CASE

A forty-seven-year-old man was admitted to the hospital because of abdominal pain and weight loss.

Four or five months before entry he experienced a severe "pulling" pain in the epigastrium whenever he lay down. Because of persistence of this pain and the onset of jaundice he consulted his physician. X-ray studies were done, and he was told that he had gallstones. Three and a half months before admission a cholecystectomy and common-duct exploration were performed. "Small stones" were found in the gall bladder. A T tube was inserted and left in place for a little over a month. Upon its removal "a cupful of old black blood" issued from the tube tract. This continued to drain "pure bile" intermittently up to the time of admission. Occasionally, there were periods of four or five days during which there was no drainage. When this occurred severe shaking chills and jaundice developed. Although the stools had been "clay colored" before operation they had been normal in color since. In addition to the epigastric pain, which became steady, he complained of pain in the right side of the chest associated with deep respiration. This too was aggravated by his lying down. Over a period of about four months he lost an estimated 60 pounds, and felt very fatigued. There had been no nausea or vomiting.

The past history was negative except for orthopnea ever since the cholecystectomy and for mild nocturia.

Physical examination revealed a thin, weak man with evidence of recent weight loss. The skin and scleras were slightly icteric. Examination of the heart revealed a Grade 2 apical systolic murmur. There was dullness over the right-lung base, with decreased breath sounds and fremitus. The level of the right leaf of the diaphragm could not be established. The abdomen showed an epigastric operative scar at the upper end of which was a small sinus tract. A small amount of clear, yellow fluid drained from this. No organs or masses were palpable. Tenderness was not demonstrated. The prostate was slightly enlarged but of normal consistence.

The temperature was 101°F. by mouth, the pulse 110, and the respirations 25. The blood pressure was 150 systolic and 85 diastolic.

The urine was alkaline, had a specific gravity of 1.018, gave a ++ test for protein and a ++++ test for bile and contained 10 white cells per high-power field and numerous hyaline and coarsely granular casts in the sediment. Examination of the blood revealed a hemoglobin of 11.8 gm. per 100 cc. and a white-cell count of 17,000, with 94 per cent neutrophils. The nonprotein nitrogen was 23 mg., the total serum bilirubin 5.9 mg., the total protein 7.1 gm., and the albumin 5.5 gm. per 100 cc.; the potassium was 4.4 milliequiv., and the chloride 93 milliequiv. per liter. The prothrombin time was 14 seconds (normal, 13 seconds). Cephalin flocculation was + and ++ at twenty-four and forty-eight hours respectively. A stool was negative for blood (guaiac test) and bile. X-ray studies of the chest revealed a large accumulation of free fluid in the right pleural cavity, and some shift of the mediastinum to the left.

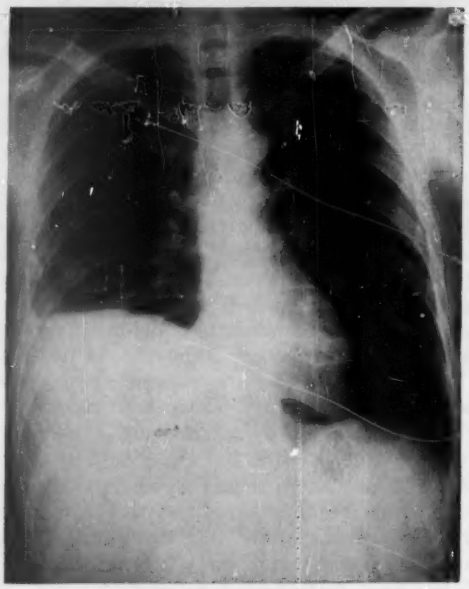

FIGURE 1. *Posteroanterior Roentgenogram of the Chest after Partial Removal of Pleural Fluid on the Right, Showing Elevation of the Right Leaf of the Diaphragm.*
The heart is normal in size, and there are no congestive changes in the lungs.

After the first day the patient's temperature dropped to levels of 99 to 100°F. and remained there. He was placed on a high-protein diet with vitamin supplements and received sedation at night, but on only one occasion did he require an analgesic because of pain. Five hundred cubic centimeters of serosan-

guineous fluid was withdrawn from the right side of the thorax on the fourth hospital day. Preparations for cytologic study of both the pleural fluid and the fluid draining from the abdominal sinus tract were reported as "unsatisfactory." After the chest tap an x-ray film of the chest again revealed right pleural fluid but much less than that present previously (Fig. 1). A density above the fluid level was interpreted as atelectasis. The patient remained weak and had considerable difficulty trying to take the high-protein

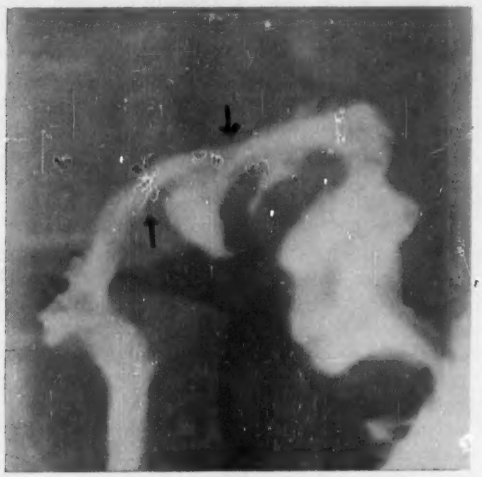

FIGURE 2. *Spot Film, Showing Deformity of the Duodenum, with Narrowing at the Apex of the Duodenal Bulb and of the Proximal Second Portion (Arrows).*

diet offered him. On the seventh hospital day an upper gastrointestinal series was done. The right leaf of the diaphragm was elevated. The esophagus and stomach were not remarkable. The duodenal cap was markedly deformed, without evidence of ulceration (Fig. 2). The proximal portion of the descending limb of the duodenum was contracted and spastic, but no obstruction to the outflow of barium was manifest. The duodenal mucosa appeared intact. There were linear strands of increased density above the duodenal bulb. Leukocytosis persisted. On the ninth hospital day tenderness and marked resistance were observed in the right midepigastric region. Some tenderness was also present over the right twelfth rib and eleventh interspace laterally. The patient was prepared for surgery with multiple blood transfusions. An operation was performed on the tenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MARTIN B. LEVENE*: This patient, after cholecystectomy and common-duct exploration, had a persistent biliary fistula, obstructive type of jaundice, occasional episodes of what I interpret to be cholangitis and the signs and symptoms of disease in the right pleural space. I cannot gain any help from the atypical pain that first sent the patient to a physician before admission. It is of interest that small stones were present in the gall bladder at operation; since these are the type that commonly give trouble by entering the common duct, they probably caused the jaundice and the clay-colored stools before admission. I am not told what was found in the common duct at operation, but presumably one or more stones were removed. Nor am I told whether an operative or postoperative cholangiogram was done. I think we can assume from the postoperative course that one or more stones were left behind in the biliary tree. The two alternatives to this diagnosis are an obstructive neoplasm and a common-duct stricture, each of which may produce jaundice. The intermittent attacks of jaundice suggest that there was a ball-valve mechanism present. I think I can deduce from the history that possibly there was a stone that shifted considerably so that at times, when it was distal to the fistula, drainage from the fistula took place; and when it was proximal and blocked the passage to the fistula there was no drainage, and chills and fever occurred. Last year during an intravenous cholangiogram I had the opportunity to observe a stone moving around in the duct. On the early film two small stones were seen in one of the hepatic ducts; as the examination progressed, after the patient was put in the upright position, the films made showed that one of the stones had migrated to a point approximately in the vicinity of the ampulla and that the duct had become somewhat dilated.

I think now would be a good time to look at the roentgenograms. The initial films of the chest reveal an accumulation of fluid in the right pleural space. It is impossible to be certain about the level of the right leaf of the diaphragm. The heart and the mediastinum are shifted slightly to the left. After the removal of the fluid (Fig. 1) the films show the decrease in fluid as expected and a band of increased density in the right-lower-lung field, which I interpret as atelectasis. These subsequent films give a good opportunity to observe the heart size, which I believe is within normal limits. That is helpful in ruling out heart failure as a cause of the fluid in the pleural space.

In several of the films of the abdomen, I notice a small, rounded density lying somewhat above and slightly anterior to the duodenal cap. This lies in the proper location for a stone in the common duct or possibly in a hepatic radicle. The duodenal cap is contracted and never fills out well (Fig. 2). Was this deformity due to a healed ac nt duodenal ulcer or to inflammation in the region? The descending portion of the second part of the duodenum is narrowed, and yet there is no evidence to suggest a pancreatic neoplasm. One of the earliest signs of such a lesion is flattening of the medial folds of the second portion of the duodenum, with turning up

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and compression of their ends to form a thin, white line along the medial border. Other signs that point to a neoplasm of the head of the pancreas are elevation of the antral portion of the stomach or the duodenal cap or in the later stages, the so-called reverse-3 sign, which consists of compression of the proximal and distal portions of the medial aspect of the second portion of the duodenum; the point at which the ampulla lies is not so easily compressed, thus giving rise to the sign. There is no evidence of any of these signs in the case under discussion. A few unusual strands of linear density are present in only two films of the abdomen; I have chosen to regard these as artifacts since a film of the same region made the next day fails to show them. On this film of the abdomen the tissue planes in the right side of the abdomen are not clearly defined; on the left side the kidney shadow and psoas-muscle shadow are well seen, but on the right side even though the barium obscures only the lower portion of the field the upper portion of the psoas-muscle shadow and the upper pole of the right kidney are not seen. On this film the level of the diaphragm is visible, and it certainly is high. This was confirmed at fluoroscopy when the gastrointestinal series was done. It would be helpful to know if there was any limitation of motion of that leaf of the diaphragm. Possibly I might have gained additional information by a plain film of the abdomen taken before contrast medium was given, which I strongly recommend, and an intravenous cholangiogram. This patient may not have excreted enough contrast medium to demonstrate the common duct. In our studies[1] we found that a bromsulfalein retention of above 15 per cent usually prevented a satisfactory cholangiogram from being obtained.

At the time of admission the urine contained protein, bile, white cells and casts. Two possibilities suggest themselves: damage to the kidney by the continued excretion of bile or the effects on the kidney of an inflammatory reaction in the retroperitoneal tissues surrounding it. The patient was moderately anemic, although the hemoglobin value of 11.8 gm. per 100 cc. was probably high, because of dehydration. The high serum protein values also point to dehydration. The chlorides were low, but I think that the biliary fistula was responsible for that. I think I can limit the possibilities if I bear in mind that I am dealing with an intra-abdominal disease that was associated with right pleural disease. I do not think cardiac failure was responsible for the effusion, for there were no other signs of failure and the heart was of normal size.

Neoplasm could certainly affect both the abdomen and pleura. Carcinoma of the head of the pancreas, ampulla of Vater, common duct or possibly of the liver could produce this picture. Other possible conditions are lymphoma and metastatic carcinoma in the lymph nodes about the porta hepatis. Unfortunately, we cannot depend too much on the absence of radiographic evidence of a lesion in the head of the pancreas or ampulla. Two recent studies[2,3] of a large number of cases have shown that the diagnostic accuracy in this area is about 50 per cent. However, I should expect to see a more complete obstruction to the flow of bile into the bowel if there were a lesion either in the head of the pancreas or common duct of this duration. The lesions of the ampulla are likely to give a more intermittent type of obstruction as a result of ulceration and necrosis of the tumor. Blood in the stool, which was not found in this case, would give a clue to that type of lesion. Carcinoma of the bile duct is a relatively rare lesion; if for no other reason, I choose to put that aside. Similarly, carcinoma of the liver is rare in this country in people without pre-existing cirrhosis of the liver. In addition a carcinomatous liver is palpable in a large percentage of the cases, and the cephalin-flocculation test is usually strongly positive.

This leaves metastatic carcinoma and lymphoma to be considered. I exclude lymphoma on the basis of the absence of any other signs of this disease. The liver and spleen were not enlarged, and no peripheral lymph nodes were palpable. Metastatic carcinoma is more difficult to exclude since a small, asymptomatic primary tumor might have been present in the abdomen. The features of this case that are suggestive of neoplasm are the persistent and profound weight loss and the serosanguineous type of fluid in the right pleural space, but both may be explained in other fashions. Patients with biliary fistulas are prone to lose considerable weight rapidly. Serosanguineous fluid is by no means limited to neoplasm. In a recent study Leuallen and Carr[4] point out that in over 400 patients with pleural effusions, only 62 per cent of the bloody effusions were due to neoplasm.

Certain features of the case point to infection as the underlying pathology: the leukocytosis, the febrile course and the spasm and tenderness in the right epigastrium and flank that developed immediately postoperatively. I think we can reasonably say that this man had episodes of cholangitis, but this alone was not enough to account for the entire picture, particularly the elevation of the right leaf of the diaphragm and the pleural effusion on the right side.

I think there are similar objections to subacute or chronic pancreatitis, although the inflammatory changes in the duodenum suggest an inflammation in the region of the pancreas. There were no calcareous deposits on the films in the region of the pancreas to suggest a pancreatic inflammation of any duration.

Pyogenic liver abscess is a definite possibility. There was a good route of infection. An abscess adjacent to the right leaf of the diaphragm could provide elevation, and such abscesses do enlarge in that direction. The findings of fluid in the pleural space and atelectasis in the right lung are also consistent. I should like to see a more spiking type of fever with greater elevations of the temperature with a liver

abscess, as well as evidence of downward enlargement and tenderness of the liver.

I hesitate even to mention amebic abscess of the liver but shall for the sake of completeness. There are a fair number of cases in which it occurs without a pre-existing history of dysentery. Again, the absence of tenderness and enlargement of the liver are against such a lesion.

This leaves me with subdiaphragmatic abscess as the prime consideration. The position of the diaphragm, the collection of the fluid in the right pleural space and the physical findings before operation are all in keeping with such a lesion. The pathogenesis of such an abscess in this patient can be explained in two ways. The deformity of the duodenal cap brings to mind the possibility of a silent duodenal ulcer, which may have perforated and subsequently healed, thus providing a path of infection for subdiaphragmatic abscess. I think a more likely route, however, is from the biliary tract. There was evidence of a hematoma, for old black blood was drained at the time the T tube was removed. Such a hematoma would readily lend itself to infection, which might then spread through the retroperitoneal tissues to the subdiaphragmatic region. It also indicates to me that there may have been a fair amount of retroperitoneal inflammation in keeping with changes in and about the duodenum noted on the films. I should expect that this patient had a subdiaphragmatic abscess and a stone in the common duct.

DR. DANIEL S. ELLIS: I think it would be very helpful if we knew the findings at the time of the first operation. What did the common duct look like?

DR. BENJAMIN CASTLEMAN: Do you know, Dr. Jones?

DR. STEPHEN G. JONES: Stones were not found in the common duct when it was explored. The gall bladder was full of them. I could get the first two dilators through the ampulla of Vater but no more. The pancreas was soft, not nodular. We thought of the possibility of carcinoma of the pancreas or of the ampulla of Vater, but could find no evidence of either. There were signs of inflammatory reaction in the region, and the patient was quite sick. We inserted a T tube with the hope that the inflammation might subside and that the stricture or whatever it was might open up. Bile was evidently getting through into the intestine, but not fast enough, and back pressure kept the common-duct sinus open.

DR. ELLIS: Was there a possibility that the mass that you saw after the fluid had been removed was a tumor rather than atelectasis in the chest, Dr. Levene?

DR. LEVENE: The fact that the density cleared at intervals over the three-day period indicates that it was probably lung that re-expanded.

DR. ELLIS: If one postulates that this patient had infection and subdiaphragmatic abscess as a cause of the findings after the second operation, one also has to postulate another cause for the original jaundice. One diagnosis that might logically explain the whole picture is carcinoma either in the liver or in the pancreas causing obstruction at the ampulla of Vater that produced the serosanguineous fluid. I think cholangitis due to obstruction of the common duct persisted and resulted in a biliary fistula. I should be more inclined to favor carcinoma of the ampulla of Vater, which gives an intermittent type of jaundice, and metastatic abscess of the liver or tumor of the dome of the liver, which would account for the appearance of the x-ray film of the chest.

CLINICAL DIAGNOSES

Subdiaphragmatic abscess.
Choledocholithiasis.

DR. MARTIN B. LEVENE'S DIAGNOSES

Subdiaphragmatic abscess.
Choledocholithiasis.

ANATOMICAL DIAGNOSIS

Colloid adenocarcinoma of head of pancreas or common bile duct, with metastases to regional lymph nodes.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Jones, would you like to tell us what you found at the second operation?

DR. JONES: When we opened the abdomen the right upper quadrant was a mass of adhesions; it was difficult to expose the common-duct region. The fistula led close to the liver and was draining clean bile. The liver and diaphragm were perfectly clean. The duct was opened and was found to be full of tumor. The pancreas was obviously cancerous. We opened the duodenum, and even a small probe could not enter the ampulla of Vater. We found one lymph node about 1 cm. in diameter that contained metastatic carcinoma. We closed the opening of the duodenum, putting a T tube in the right hepatic duct, and closed the wound.

DR. CASTLEMAN: Do you think the shadows that suggested the subdiaphragmatic abscess were caused by the adhesions?

DR. JONES: I believe that back-pressure kept the fistula open and that bile was getting through, but not enough. I assume that the appearance of the diaphragm might have been due to insult from the bile collecting under it when the fistula occasionally closed over at the skin or subcutaneous-tissue level and thus blocked the free drainage of bile.

DR. CASTLEMAN: The biopsy of the lymph node showed metastatic adenocarcinoma that apparently arose from the primary tumor, which may have been in the pancreas or in the common duct.

DR. EDWARD DUNN: In trying to tell whether the

large irregular lesion in the head of the pancreas was cancer or pancreatitis, we felt the pancreatic duct. Cattell and Warren[5] state that when the pancreatic duct is distended, as it was here (a large turgid pancreatic duct on the anterior surface of the pancreas), that is presumptive evidence of cancer in the head of the pancreas.

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CASE 41262

Presentation of Case

A fifty-five-year-old retired postal clerk entered the hospital with the complaint of visual impairment.

Six months before entry the patient consulted his physician because of dull pains in the calves at night and after exertion during the day. Urinalysis was positive for sugar at this time, and a carbohydrate-free diet was prescribed. Two months later he began to notice decreasing visual acuity. Six weeks before entry, he consulted an ophthalmologist, who diagnosed diabetic retinopathy and finally referred him to this hospital.

He had been obese since the age of eighteen (maximum weight 240 pounds) and had had leg cramps, polydipsia and nocturia (one time) for five years. There was a history of a moderately heavy intake of alcohol. Otherwise, he was well.

The temperature was 99.6°F., the pulse 90, and the respirations 22. The blood pressure was 170 systolic, 70 diastolic.

Physical examination revealed an obese man in no distress. There was slight cardiac enlargement and a precordial Grade 2 systolic murmur. The liver was palpable 3 or 4 fingerbreadths below the right costal margin, and the spleen was "easily palpable." Rectal examination showed slight nodular enlargement of the prostate and internal hemorrhoids. There was ++ pitting edema of the legs up to the knees and some sensory impairment in the distal extremities. The eyegrounds showed marked diabetic retinopathy with hemorrhage and exudates.

The urine was clear, had a pH of 6 and a specific gravity of 1.021, gave a green test with precipitate for sugar and negative tests for albumin, acetone and bile; the sediment was unremarkable. Examination of the blood revealed a hemoglobin of 9.5 gm. per 100 cc., a white-cell count of 4400, with 49 per cent neutrophils, 22 per cent lymphocytes, 8 per cent monocytes, 11 per cent eosinophils and 1 per cent basophils, and a reticulocyte count of 2.2 per cent. A smear showed slight hypochromia and microcytosis of red cells. The serum iron was 60 microgm. per 100 cc. (normal, 125 to 200 microgm.), the saturation 13 per cent (normal, 33 per cent), the clotting time normal, the bleeding time 31 minutes (normal, 6½ minutes) and the clot retraction poor. A platelet count by the indirect method was 270,000 per cubic millimeter. The plasma fibrinogen was 0.44 gm. per 100 cc. The fasting blood sugar was 148 mg., the nonprotein nitrogen 27 mg., the albumin 3.6 gm., and the globulin 3.3 gm. per 100 cc. The prothrombin time, alkaline phosphatase and cholesterol levels were normal. Cephalin flocculation was ++ in twenty-four and forty-eight hours. Electrophoretic serum proteins were normal in quantity and distribution of albumin and globulin. A blood Hinton test was negative. Stool guaiac tests were positive on several occasions; on all but one of the specimens, however, gross blood was seen. An electrocardiogram showed nonspecific T-wave changes consistent with coronary heart disease. An x-ray film of the chest showed enlargement of the left ventricle and tortuosity and calcification of the aortic arch. A plain film of the abdomen revealed hepatosplenomegaly. A gastrointestinal series was negative. Sigmoidoscopy revealed a bleeding internal hemorrhoid and fissure-in-ano. A barium-enema examination showed a defect medially in the ascending colon just distal

Figure 1. *Initial Barium-Enema Examination, Showing a Suggestive Intraluminal Defect of the Proximal Ascending Colon (Arrow).*

to the ileocecal valve, having the appearance of an intraluminal mass (Fig. 1). A second barium-enema examination five days later revealed a suggestive intramural extramucosal defect of the ascending colon in the same location and in addition a similar type

FIGURE 2. *Barium-Enema Examination Five Days Later, with the Deformity of the Ascending Colon Again Evident (Upper Arrow).*
There is also a suggestion of an intramural extramucosal mass in relation to the superior aspect of the terminal ileum (lower arrow).

of deformity involving the superior aspect of the terminal ileum (Fig. 2).

The patient was treated with a diabetic diet and insulin. On the twenty-fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. STEPHEN M. KRANE*: This fifty-five-year-old patient came in with symptoms of diabetes and presumably complications thereof. On admission he was found to have hepatosplenomegaly, bleeding hemorrhoids, prostatic enlargement, positive stool guaiac tests, edema, anemia, leukopenia, thrombocytopenia and eosinophilia. In addition on x-ray examination a mass was noted in the region of the cecum. He gave a history of polydipsia and nocturia dating back about six years, which was suggestive of diabetes, but the disease was not diagnosed until about six months before admission, when the blood sugar was 148 mg. per 100 cc. and the green test for sugar in the urine confirmed the diagnosis. The nocturia was perhaps related to the nodular, slightly enlarged prostate. The cramps that he had with exertion and rest are suggestive of arterial insufficiency in the legs; however, the impairment of the sensation in the legs raises the question of diabetic neuropathy. There was no mention of the pulses in the extremities. The decrease in visual acuity could be explained on the basis of diabetic retinopathy. In view of the finding of decreased platelets and prolonged bleeding time, however, I wonder what part the blood dyscrasia may have played in producing the retinopathy.

This man was obese on entry; he previously had weighed 240 pounds. Had he lost any weight before he came in, Dr. Castleman?

DR. BENJAMIN CASTLEMAN: Do you know, Dr. Jones?

DR. CHESTER M. JONES: I think he had lost some, not a large amount of weight.

DR. KRANE: The temperature on admission was 99°F.; I wonder whether he had any fever during the stay in the hospital. The systolic blood pressure was elevated but diastolic pressure was normal and there was electrocardiographic evidence of coronary disease. Those findings fit with the enlargement of the left ventricle and the calcification of the aortic arch noted on the x-ray film. Aside from the ++ edema of the legs there was nothing to suggest heart failure. The liver was palpable 3 or 4 fingerbreadths below the right costal margin but was not further described; I assume that it was enlarged. The spleen was easily palpable. There was no mention of pigmentation of the skin, adenopathy, jaundice or vascular spiders.

The blood picture was decidedly abnormal; the hemoglobin was 9.5 gm., with a microcytic hypochromic anemia, and the serum iron was low along with a decrease in the saturation of the siderophilin and a high iron-binding capacity, which I should calculate to be 462 gamma per 100 cc. The blood findings are compatible with blood-loss anemia rather than the anemia of chronic infection or a malignant process, in which the serum iron and total iron-binding capacity are reduced. The reticulocyte count of 2.2 per cent is also compatible with a blood-loss anemia, and, although a hemolytic element may have played a part, there was no direct evidence of it. There was a slight leukopenia, with a definite absolute neutropenia, some monocytosis and a definite eosinophilia. I wonder whether the low white-cell count and the eosinophilia were confirmed on more than one examination. By the indirect method the platelet count was 270,000, which is definitely decreased, the normal being between 500,000 and 1,000,000. The poor clot retraction and the prolonged bleeding time are corroborative of the platelet deficiency.

DR. CASTLEMAN: Apparently, only one blood smear was done. All the white-cell counts were about 5000.

DR. KRANE: The tests of liver function were negative except for the slightly increased globulin and reduced albumin done by the Howe method. The fibrinogen was somewhat increased. I wonder if I could see the x-ray films.

*Clinical and research fellow in medicine, Massachusetts General Hospital.

DR. C. C. WANG: The lung fields are clear; the heart is somewhat prominent in the region of the left ventricle; and the left leaf of the diaphragm is higher than usual, presumably as a result of the enlarged spleen. Two barium-enema examinations, performed in a period of five days, confirm a lesion in the proximal colon. There appears to be a small polypoid filling defect, measuring approximately 3 cm. in greatest diameter, in the medial aspect of the ascending colon. In addition there is a smooth pressure defect in the medial aspect of the proximal colon just above the ileocecal valve.

DR. KRANE: What represents the intramural defect?

DR. WANG: This pressure defect has the appearance of an intramural extramucosal tumor.

DR. KRANE: Is there calcification in the middle of that?

DR. WANG: No; the calcifications are probably in the abdominal lymph nodes. There is also a smooth extrinsic pressure defect at the superior aspect of the terminal ileum, approximately 4 cm. proximal to the ileocecal valve. This also has the appearance of an intramural extramucosal tumor. I do not see any evidence of ulceration in the terminal ileum.

DR. KRANE: Is there ulceration over the mass producing pressure medially?

DR. WANG: I cannot be sure.

DR. KRANE: Do you see any evidence of esophageal varices?

DR. WANG: A barium-swallow examination shows perfectly smooth esophageal folds and no evidence of esophageal varices.

DR. CASTLEMAN: Do you think that there are two masses?

DR. WANG: There are at least two masses that appear to be intramural and extramucosal, one involving the ascending colon and the terminal ileum; there may be in addition an intraluminal polypoid defect of the ascending colon.

DR. KRANE: It seems to me that there are roughly three problems: the first is the diabetes, which I should believe was diabetes mellitus with retinopathy and probably neuropathy associated with some degree of coronory-artery disease and arteriosclerosis — as evidenced by the cardiogram and the calcification in the aortic arch; the second is the hepatosplenomegaly, the blood picture compatible with hypersplenism and the eosinophilia; and the third is the masses not only in the ascending colon but also probably in the terminal ileum, with probably an associated blood loss.

I find it difficult to associate the diabetes with the other problems. The question of hemochromatosis might be raised in a patient with a large liver and spleen and diabetes. The associated findings, however, were not present; the serum iron was low, and the serum iron-binding capacity was high with unsaturation, which would rule out that diagnosis. Also, with diabetes, hepatosplenomegaly, eosinophilia, a lesion in the cecum and calcified mesenteric lymph nodes, tuberculosis has to be considered. It occurs with somewhat increased frequency in diabetic patients. Moreover, tuberculosis of the spleen has been described as producing the entire picture of hypersplenism. Even eosinophilia has been reported in tuberculosis with extensive caseation. Tuberculosis may involve the bowel, and the hyperplastic type can give lesions sometimes not easily distinguished from those of carcinoma. The lesions often involve the terminal ileum and the cecum so it would be perfectly possible that the lesion producing the deformity there, aside from the polyp, was explainable on the basis of tuberculosis. The calcified lymph nodes tell me that this patient had been infected at one time. Although I did not favor this diagnosis when I studied the protocol, it is a good possibility.

I do believe I have to relate the hepatosplenomegaly and the lesion in the ileum. The patient was an alcoholic, so the question of cirrhosis is raised. There were no esophageal varices, nor was there evidence of portal hypertension to explain the splenomegaly, but these certainly are not necessary. The blood picture of hypersplenism has been described in cirrhosis. However, this diagnosis offers no way of explaining either the eosinophilia or the mass in the cecal area. The usual causes of congestive splenomegaly, except possibly metastatic tumor thrombosis in the portal vein or occasionally thrombosis associated with tumors, I do not believe are likely. Sarcoidosis produces eosinophilia, hepatosplenomegaly and this sort of blood picture, but I am unable to find any evidence that sarcoidosis has ever produced such a lesion of the bowel as was described here. In their review Longcope and Freiman[1] said that they would not accept any lesion so described. Amyloidosis also rears its head here, but I have no way of making this diagnosis. Multiple myeloma can give eosinophilia, hepatosplenomegaly and a blood picture of this sort. The normal electrophoretic pattern of the serum is against that diagnosis, but certainly does not rule it out. Again, I was not able to find any reference to myelomatous tumors involving the bowel.

I assume that this man was never outside the United States and was not exposed to diseases like echinococcosis. Parasitic diseases that would produce this picture are unusual. Ascariasis can produce a bolus that causes obstruction, but it would not give this particular configuration nor would it explain the enlarged liver and spleen. Amebiasis can occasionally produce a lesion in the cecum without lesions elsewhere in the colon. It is my understanding that when amebiasis does do this it is associated with symptoms. There was never any history of diarrhea. The liver disease of amebiasis is usually associated with tenderness and a leukocytosis rather than a leukopenia. I have no evidence for the granulomas that could produce this. In this part of the country histoplasmosis would be distinctly unusual.

Could he have had a primary tumor in the cecum that metastasized to the liver? I should think that a lesion from carcinoma of the ileum metastatic to the liver that produced secondary splenomegaly, without affecting the size of the liver more than this and without causing functional abnormalities, would be extremely unusual. Nor would it explain the eosinophilia, if the eosinophilia was pertinent. Carcinoid can involve both the ileum and cecum and may metastasize widely in the abdomen and to the liver. In articles written since the recent revival of interest in this particular tumor, abnormalities in the skin and circulation with carcinoid have been mentioned. Almost all the patients have had symptoms referable to the gastrointestinal tract.

The diagnosis that I think is the most logical, in spite of the fact that there was no peripheral adenopathy, fever or significant weight loss, is Hodgkin's lymphoma. Hepatosplenomegaly is common, however. The blood picture is compatible with this condition — the neutrophilia, the eosinophilia, which occurs in about 20 per cent of cases, the slight monocytosis and the elevation of the serum fibrinogen, which is certainly not specific. Hodgkin's disease or other lymphomas can involve the cecum; of 50 cases reviewed at the Mayo Clinic[2] in 1933, 18 lymphomas appeared in the cecum, which was the commonest single location in the intestinal tract. They rarely erode and can produce an intramural defect, without erosion of the mucosa. The leukemia group would fit in with this, but I have no evidence for that. I am confused by the appearance of the lesion in the ileum, but I shall stick to my original impression, which was that the patient had a malignant lymphoma involving the spleen, liver and cecum and possibly the iliac lymph nodes to account for the edema, in addition to diabetes mellitus with retinopathy and neuropathy.

DR. JONES: We thought on the Service that this man had diabetes mellitus, that he may have had nephropathy that was not interfering too much with renal function and that he had cirrhosis. There was a tumor or a defect demonstrated, which I thought was extraluminal rather than intraluminal and was probably not carcinoma of the cecum. He had an anemia, which was exaggerated by blood loss and which we could not explain except on the basis of frank erosion of the cecal lesion. The important thing was to find out by exploration what the tumor was and to remove it if possible. At the same time we realized that he had liver disease and that any operation would carry a risk so that all precautions would have to be taken to make a difficult operation as safe as possible.

CLINICAL DIAGNOSES

Tumor of cecum.
Cirrhosis.
Anemia.
Diabetes mellitus.

DR. STEPHEN KRANE'S DIAGNOSES

Lymphoma of cecum, with involvement of liver and spleen.
Diabetes mellitus, with retinopathy and neuropathy.

ANATOMICAL DIAGNOSES

Carcinoid of terminal ileum.
Portal cirrhosis of liver.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The first procedure was a needle biopsy of the liver, which showed a portal cirrhosis of the Laënnec type.

Aware of the hazard of operating on a patient with portal hypertension, the surgeons decided to explore the cecal region with the plan to resect the terminal ileum, cecum and ascending colon. At operation the only point of obstruction found was in the terminal ileum. A careful exploration of the region of the intraluminal lesion in the acending colon observed on the x-ray films did not disclose any abnormality. A resection of only the terminal ileum was done. The obstructing lesion in the ileum proved to be a carcinoid that involved the muscularis and mucosa, appearing in the lumen as multiple excrescences without definite ulceration (Fig. 3). Microscopical sec-

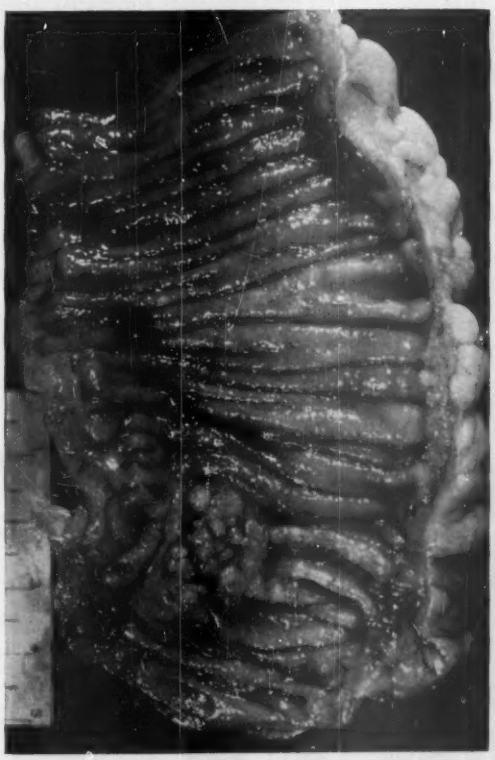

FIGURE 3

tion showed normal mucosa, with carcinoid infiltrating the wall and in one area, in which there was a great deal of polymorphonuclear infiltration and necrosis, destroying the mucosa. There may have been mild oozing from this carcinoid. Although carcinoids in general are not supposed to ulcerate, we have had 1 or 2 that have ulcerated, with a great deal of bleeding.

DR. WANG: I think the appearance of the ascending colon is definitely abnormal. I am afraid that there are lesions left behind in the proximal colon.

DR. CASTLEMAN: Can anyone tell us about the operation?

DR. OSCAR E. STAROBIN: At operation the surgeons could only do a limited resection because of the marked bleeding tendency. All the mesenteric veins were widely dilated, and there was portal hypertension. The defect in the ascending colon just above the ileocecal valve was thought to be caused by an inflammatory reaction perhaps secondary to the adjacent carcinoid, although a metastasis from the carcinoid is a possibility.

DR. CASTLEMAN: Dr. Frank W. Garran, who operated on this patient, informed me that he was quite certain it was not a metastasis.

DR. JONES: I should like to point out that evidence of cirrhosis points out danger in any abdominal operation. The surgeon frequently cannot operate as he would choose because of the tremendous vascularity, the portal hypertension and the difficulty in producing hemostasis. Every venule is a vein, and every capillary is a venule, so to speak.

DR. CASTLEMAN: The patient left the hospital and when last seen six weeks postoperatively in the Clinics he had no complaints.

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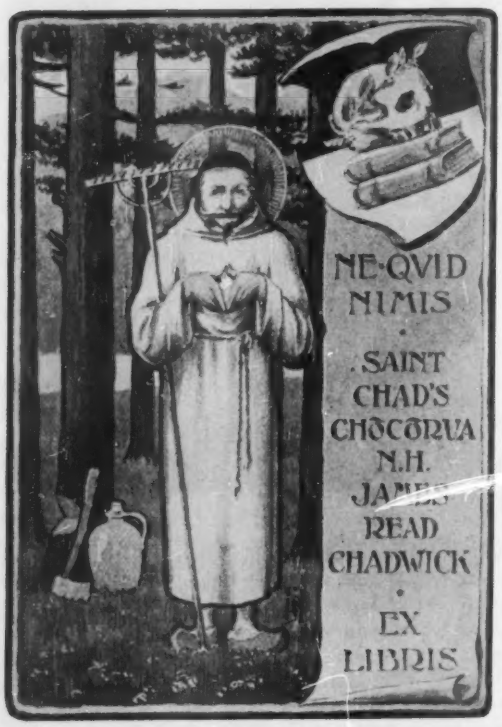

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5. Bookplate of James Read Chadwick, M.D., founder and first librarian of the Boston Medical Library, and eminent gynecologist. The bookplate depicts the Saint of Chocorua, Dr. Chadwick's favorite spot in New Hampshire, where he had a summer residence on Mount Chocorua.

The New England
Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

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WATERS OF THE FLOOD

THE inundation of solid land by water has been one of the catastrophes that have periodically overtaken man and beast since first the waters receded and the resulting terrain became inhabited. The account given in Genesis of the forty days and forty nights during which the rains fell is the dramatic and classic example of a flood that was a flood; that something like it has happened, perhaps repeatedly, is written in the timeless records that geologists have discovered and defined.

The perfect example of boredom is attributed to Noah, when, long a celestial resident, he was forced to listen to the experiences of a recently arrived victim of the Johnstown flood. Not all floods are unwelcome; in addition to those resulting from extraordinary natural conditions and from nature's restiveness under the restraints that man has imposed are the expected and beneficent flooding of arable lands, as along the lower Nile. Here man has wisely made use of a natural phenomenon rather than trying to oppose it.

In contrast to the tragic experiences in England and the Netherlands in recent years when the ocean itself successfully assaulted the low countries, the United States has experienced a marked decline in the yearly loss of life in floods. The subject is one toward which the tireless statisticians of the Metropolitan Life Insurance Company have turned their slide rules, with interesting and salubrious results.

According to this authoritative source, 1728 flood fatalities were reported by the United States Weather Bureau for the twenty years from 1934 through 1953, of which 1153 occurred during the first decade and only 576 in the second half of the period. Provisional data at the time of release, in April of this year, indicated that less than 50 lives were lost through floods in 1954; half of these occurred during the Texas flood in June.

No gigantic overflow in which as many as 100 persons have perished has occurred for more than fifteen years, according to the statistical reports, although in the period from 1935 to 1937 there were three such catastrophes. The flood season, beginning in April, continues through July, the country's important flood area consisting of the Ohio and Missouri River systems, which between them have accounted for nearly half of the total loss of life for the twenty years under consideration.

Much of the reduction in flood fatalities can be attributed to the activities of the Army engineers in constructing a complicated system of reservoirs, levees, flood walls and canals along our great rivers. Some, at least, of the extensions of the system have been made necessary by man's perversity in attempting in the first place to control the natural phenomenon of rising rivers and flooded low lands. More devastating floods attend the breaching of the levees on an elevated river system than were presumably ever en-

countered by the natural flooding of its banks. "After me, the deluge," could be attributed to the original levee builder. The corollary might well be supplied by the Red Cross — "After the deluge, me."

INVOLUNTARY ENCYSTMENT

A YEAR ago an editorial published in the *Journal** commented on the risk to young America of the discarded refrigerator, and the number of fatalities due to this death trap since records have been kept. Between 1948 and 1953, inclusive, 59 boys and 20 girls had perished as a result of accidental incarceration in such airtight and sound-proof cells, 1 to 5 children having lost their lives in each of nearly 50 incidents.

The so-called Discarded Refrigerator-Freezer Safety Campaign set in motion by the Household Refrigerator and Farm and Home Freezer Sections of the National Electrical Manufacturers Association is bearing results, however. The toll of 29 deaths in 1953 had dropped to 11 in 1954, with 2 recorded for the first two months of 1955.

Still America's prosperity continues to have its potentially disastrous side effects, and the sale of new refrigerators involves almost automatically the discarding of nearly a million old ones each year. Since each wave of prosperity will follow its own course and come to its own end little influenced by the prophets either of economic disaster or of continued gracious living, the best way to save young lives is to unspring these particular traps. This is accomplished by unhinging the doors, removing the gaskets, dismantling the latches or blowing the whole thing up, and the labor involved will be undertaken only as the result of an impressively effective educational campaign.

NOTE ON LEAD POISONING

RELATIVE to the untimely death of G. G. Bushman, of Lincoln Park Zoo, Chicago, recorded in these columns, and the subject of gorillas in general, whether *Gorilla gorilla* or *Gorilla hamana*, it seems pertinent to make some note of the interesting case of Irvin Young.[1] It transpires that Irvin, nine years of age and a resident at the same address, first developed symptoms of a neurologic disorder on May 29, 1954.

His arms being apparently affected by pain or palsy, he was forced to eat with his toes or by bending over and picking up the food with his mouth. Examination by Dr. Fisher, zoo veterinarian, and two consultants from the University of Chicago medical staff suggested a peripheral neuritis; however, examination was limited to its first phase, the importance of which is early emphasized to medical students — inspection — from without the cage.

At this stage the value of an adequate history was demonstrated; it appeared that nearly two months prior to the onset of his illness young Irvin (Irvin Young) had eaten red lead paint from the bars of his outsize crib. Since the patient was unco-operative in the matter of examination of the gums, and blood smears are sometimes difficult to obtain from resistant nine-year-olds, further investigations were limited to analysis of the urine for lead. This was found to be present at a level of 0.290 mg. per liter on a specimen collected on May 30, and 1.235 mg. on a June 4 specimen. Such positive findings may be considered of significance despite the unorthodox method of collecting specimens — mopping the urine from the cage floor with a clean plastic sponge and squeezing it into a suitable receptacle. The presumptive cause of his illness having been removed, Irvin is reported as doing nicely.

According to the director of health and safety of the Lead Industries Association,[2] cattle, horses, pigs, dogs and ducks are all represented in his case records on plumbism, but Young is the first inhabitant of a zoologic garden to enter the archives.

REFERENCES

1. Fisher, L. E. Lead poisoning in gorilla. *J. Am. Vet. M. A.* **125**: 478, 1954.
2. Bowditch, M. Personal communication.

*Editorial. Death in icebox. *New Eng. J. Med.* **251**:79, 1954.

Communications Received. — *Case of Double Pneumonia; Case resembling Tetanus; Review of Dr. Tyler Smith on Leucorrhoea; Case of Infantile Syphilis; Life Insurance Companies, and their Treatment of the Medical Profession.*
Boston M. & S. J., *July 5, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

AMNIOTIC-FLUID EMBOLISM, WITH LACERATION OF THE UTERUS

A thirty-seven-year-old gravida VI, para V, died undelivered three hours after admission to the hospital about two weeks after the calculated date of delivery. She had been known for fifteen years to be mildly hypertensive, nervous and overweight and of limited intelligence.

She had made only one prenatal visit during the entire pregnancy, in the sixth month, with a blood pressure of 180 systolic, 90 diastolic, weighing 70.8 kg. (height, 152 cm.); the urine was negative for sugar and albumin. This was the last time in her life that the blood pressure had been taken. Her physi-

cian made six telephone calls, without avail, urging her to return for additional visits. Three subsequent specimens of urine, all negative for albumin, were brought to the office by a son; the last was three weeks before death. A proprietary remedy to reduce the blood pressure was dispensed at the first visit, and additional supplies were sent home with the child. At the time of the telephone calls, the patient denied headaches, scotomas or the presence of edema.

She was admitted to the hospital at 2:45 a.m., presumably in labor, complaining with increasing bitterness of abdominal pain, but there seems to have been considerable doubt about the character or quality of contractions if any, and she was given 1 minim of pituitary extract after a vaginal examination revealed no dilatation. She was so noisy that the fetal heart could not be made out, and the physician assumed that the baby was dead. The head was floating, and the abdomen was not tender. There was no hemorrhage at any time. At 5:30 she vomited with such violence that the membranes ruptured; immediately thereafter she was noted to have poor color, with a rapid weak pulse. Soon convulsions began, continuing until death within about ten minutes.

At autopsy the lungs weighed 450 gm. each, showing moderate congestion and edema; a small amount of gray, amorphous material extruded through the cut ends of the blood vessels in the parenchyma, proving microscopically to be massive amniotic-fluid embolus. A laceration was found in the lower uterine segment, involving only the inner layers of the myometrium (about a third), and was 5 or 6 cm. long; it was fresh and irregular. The blood in vessels of the body was fluid, with no evidence of coagulation; it was watery and cyanotic. Unfortunately, sections of the uterus were not taken for microscopical study, and chemical studies were not done on the blood.

The death was classified as a preventable death, the primary cause being amniotic-fluid embolism and the contributing causes being laceration of the uterus due to the unwarranted administration of pituitary extract.

In explanation it should be clear that amniotic-fluid embolism is not necessarily always a nonpreventable cause of death since the fluid must get into the blood stream in some manner. In this patient it reached that location through a laceration of the uterus that did not penetrate its whole thickness but was undoubtedly caused by the tetanic contractions resulting from the administration of the pituitary extract. A study of the nurse's notes revealed that the patient's pains were almost continuous at the time the drug was given; the fact that she was crying aloud in pain confirms this. The administration of pituitary extract is particularly dangerous when the presenting part is unengaged, as it also was at this time.

Furthermore, prenatal care was disgracefully inadequate, although this fact probably did not contribute directly to her death. Even though the fault for this inadequacy lay with the patient the physician should have insisted on better co-operation and, in fact, should have declined to accept responsibility if compliance was not forthcoming.

JOHN FIGGIS JEWETT, M.D.
Chairman

DIRECTORY OF FELLOWS

A new *Directory* of the officers and fellows of the Society has been published, corrected to January 1, 1955.

Copies are available to all fellows who apply to the Secretary, 22 Fenway, Boston 15.

ANNUAL GOLF TOURNAMENT

The results of the 1955 Massachusetts Medical Society Golf Tournament at Dedham Country and Polo Club on May 18 are as follows: first gross, Dr. William R. Hill, Jr.; second gross, Dr. Richard S. Nugent; low net, Dr. Salvatore J. Messina; second net, three-way tie, Dr. James T. Riley, Dr. Charles G. Shedd and Dr. George R. Gagliardi.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1955

RÉSUMÉ

DISEASE	MAY 1955	MAY 1954	SEVEN-YEAR MEDIAN
Chancroid	2	1	3
Chicken pox	2169	1569	1844
Diphtheria	2	7	10
Dog bite	1707	1504	1443
Dysentery, bacillary	23	7	6
Encephalitis, infectious	6	3	3
German measles	642	1045	1045
Gonorrhea	150	168	175
Granuloma inguinale	0	0	0
Hepatitis, infectious	86	110	14*
Lymphogranuloma venereum	0	2	1
Malaria	0	0	1
Measles	4490	2853	2385
Meningitis, meningococcal	4	9	7
Meningitis, Pfeiffer bacillus	4	2	5
Meningitis, pneumococcal	1	0	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	10	8	5
Mumps	1224	2292	1661
Poliomyelitis	3	5	4
Salmonellosis	25	47	11
Scarlet fever	1469	477	519
Syphilis	142	148	182
Trichinosis	0	2	1
Tuberculosis, pulmonary	201	150	193
Tuberculosis, other forms	14	14	14
Typhoid fever	2	0	2
Undulant fever	1	0	1
Whooping cough	127	194	147

*Six-year median.

COMMENT

Diseases below the seven-year median were diphtheria, German measles, meningococcal meningitis, mumps, poliomyelitis and whooping cough.

Only 2 cases of diphtheria were reported during the month of May. This is the lowest figure for this month in the history of the State.

Three cases of poliomyelitis were reported during the month of May. The total for the year so far is 8. This is the lowest figure for this five-month period since 1950.

Diseases above the seven-year median were chicken pox, bacillary dysentery, infectious hepatitis, measles, salmonellosis and scarlet fever.

Infectious hepatitis during May was considerably above the median. However, the figure for May is below that of

the same month for the previous two years. Also in four of the previous five months the figure was below that of a year ago. It appears, therefore, that as far as reporting is concerned the "normal" incidence of the disease in the State has been reached.

During May scarlet fever was at its highest incidence for any month since May, 1945.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Adams, 1; Boston, 1; total, 2.

Dysentery, bacillary: Boston, 3; Hamilton, 1; Quincy, 2; Sudbury, 11; Tewksbury State Infirmary, 1; Waltham, 3; Wenham, 1; Worcester, 1; total, 23.

Encephalitis, infectious: Fall River, 1; Fitchburg, 1; Natick, 1; Townsend, 1; Worcester, 2; total, 6.

Hepatitis, infectious: Arlington, 1; Barre, 1; Belmont, 2; Boston, 12; Brookline, 1; Cambridge, 3; Chelsea Naval Hospital, 5; Chicopee, 1; Dartmouth, 1; Dracut, 1; East Bridgewater, 1; Fall River, 6; Grafton, 1; Hardwick, 1; Haverhill, 1; Holyoke, 1; Lowell, 2; Milford, 2; Montague, 1; Natick, 3; New Bedford, 1; Northfield, 1; Norwood, 2; Reading, 1; Seekonk, 1; Sharon, 7; Shrewsbury, 1; Somerville, 1; Springfield, 3; Waltham, 11; Wellesley, 3; West Newbury, 1; Westwood, 1; Worcester, 4; Wrentham, 1; total, 86.

Meningitis, meningococcal: Arlington, 1; Brockton, 1; Cambridge, 1; Holyoke, 1; total, 4.

Meningitis, Pfeiffer bacillus: Brockton, 1; Peabody, 1; Melrose, 1; Saugus, 1; total, 4.

Meningitis, pneumococcal: West Newbury, 1.

Meningitis, undetermined: Falmouth, 1; Foxboro, 1; Leicester, 1; Milford, 1; Murphy Army Hospital, 1; Newburyport, 1; Plymouth, 1; Sutton, 1; Watertown, 1; Westwood, 1; total, 10.

Poliomyelitis: Milton, 1; Newton, 1; Worcester, 1; total, 3.

Salmonellosis: Beverly, 1; Boston, 4; Brookline, 2; Hamilton, 1; Haverhill, 1; Lowell, 1; Maynard, 1; Methuen, 1; Natick, 1; Norwood, 1; Somerville, 1; Springfield, 2; Taunton, 2; Waltham, 2; Woburn, 2; Worcester, 2; total, 25.

Typhoid fever: Boston, 1; Worcester, 1; total, 2.

Undulant fever: Springfield, 1.

CORRESPONDENCE

CHOICE OF MEDICINE AS A PROFESSION

To the Editor: As you are doubtless aware, 40 per cent of the freshmen entering Harvard College express a preference for medicine as their life work, and 20 per cent do enter some medical school. In discussing this interesting situation with Charles E. Wyzanski, Jr., judge of the District United States Court and president of the Board of Overseers of Harvard University, I mentioned the article by Brody in the January 27, 1955 issue of the *Journal*, and later sent him the paper. His reply seemed to me to deserve a wider reading and I am enclosing the pertinent part of his letter.

> I thought that the autobiographical excerpts that Dr. Brody collected were a very satisfactory Gallup poll explaining the motivation of those who have entered the profession of medicine during the last century or so.
>
> But are there not some additional special factors that now operate upon the present generation of medical students and account for the sharp rise, at least at Harvard College, of the number of people who believe that they want to go to medical school? In the first place is it not true that the rate of scientific advance in medicine is as great as in any field except possibly physics, and that therefore the pure scientist excited by wonder and intellectual zest is drawn to medicine to a greater degree than his father was?
>
> Secondly, may it not be true that, compared with other callings, medicine has retained a larger degree of independence and dignity in what is getting to be an increasingly complex corporate society dominated by a managerial class and that, aware of this relative immunity of medicine from the evils of our mass society, young men who want to be their own masters seek to go to medical school?
>
> Thirdly, compared with the teaching profession, architecture, law, the ministry and most learned professions, has not the medical profession done quite well in retaining its relative financial position in the community?
>
> Fourthly, does not the study of recent class reports from college graduates reporting on their first twenty-five years reveal a surprisingly high percentage of doctors (compared, for example, with bankers, businessmen, lawyers and university professors) who regard themselves as having chosen a happy way of life?

Richard M. Smith, M.D.

Boston

A TESTIMONIAL

To the Editor: The following excerpt from a communication to me by a clergyman of my acquaintance will, I am sure, be of interest to the readers of the *Journal* as a dramatic picture of the subjective symptomatology and the patient-doctor psychology in a prolonged illness:

> Over a period of years I have been suffering from one of the most baffling ailments that afflict human beings — undulant fever. They say that in the United States there are millions who have had the disease or who have it to some degree; and many folks, including doctors, do not know they are so troubled. Once having it there is no one who can say safely it is nothing — it leaves its mark in many ways. I want to state how I [illegible], where I picked up the bug, and how it was finally diagnosed by those to whom I owe much.
>
> Along about 1943 I was sent by my superiors to a small city located in the deep South. After a year or so a terrific and chronic fatigue took hold of me. At first I thought it might be the heat, as coming out of the North, my system was not regulated to a hot climate. Time passed — the aching fatigue did not subside (even at this late date it frequently raises its ugly head.) Finally the fever came and laid me low. The local doctor said, "You have the flu"; and for a period of 2 weeks I ran a fever from 101 to 105. At long last it dropped, but not to normal. For days it would jump and for months it ran low-grade. Finally it seemed to pass but the fatigue, excessive and mysterious remained and dulled every part of me, making life a burden and a torture. Up and about I tried to do my work, but in a few days again was floored by the fever. There were headaches, backaches, and other aches in places I never knew existed — pains resembling influenza, except more severe and continued. After flu the sickness was diagnosed as malaria, typhoid fever or what have you.
>
> For more than a year I remained for months on end in pain and extreme fatigue. I did not know if I were coming or going and frankly did not care. At times the fever was low and suddenly it would jump to 103 or 104 — none of the treatments seemed to help. Rather disheartened I pleaded with the doctor to aid me and was told to spend 3 or 4 hours every afternoon resting. Even this failed to help. It was thought I might have rheumatic fever or tuberculosis, as I frequently coughed up blood. Weak, helpless, trying to work, my life was far from being rosy. After a year of this the symptoms intensified and the fever shot up again; and the local doctor sent me to a hospital some 70 miles from where I lived. He took no tests for Undulant Fever. While at the hospital it was found I had a heart condition, a liver disorder, diabetes and the flu, together with a rheumatic condition. And still no tests were made for Undulant Fever. Again the doctors said things like malaria, and tuberculosis. But whatever I had, one thing alone I know, one thing I am sure of, is that the muscles and bones pained and pained. At times it seemed as if a toothache in every joint made itself known, at others as if I had dislocated them. Over and above it all the terrible fatigue continued and day

and night the fever. After some months in bed the fever lowered; a certain rest came and I returned to work.

After five weeks more the entire process returned; and again the local doctor prescribed the same drugs and the long ride in an ambulance to the hospital. Still no tests for Undulant Fever; merely: "You have this or that — better go to Arizona."

After many months a specialist from a large city some 300 miles away came to see me. He could not spend much time, but his advice I feel saved my life. He said, "I am sorry that I am not on the staff here — I came to visit you at the request of a friend. For various reasons I cannot take charge; I can only tell you what to do. As soon as possible take yourself to Boston. Enter one of the hospitals there and I think they will find out shortly what ails you." He went on to say, "I believe you have a heart condition, rheumatic fever, arthritis and fundamentally Undulant Fever." Months later I sent him word how right he was.

As soon as arrangements were made I was flown to Boston and room was found for me at one of the leading hospitals. Now comes what to me is the miraculous part and I believe it is due to the studies made and the personal interest of the physicians. A whole series of tests was made, and wonder of wonders and God bless the good doctors in that hospital, in five days they diagnosed the illness — undulant fever. The cause was drinking raw milk.

I have spent years in hospitals and abed, and have suffered long. I have been a first class guinea pig, and have had all the new wonder drugs; but I find that the old saying is still true: "An ounce of prevention is worth a pound of cure." The best preventive medicine is the use of pasteurized milk and the products made by it. In most sections of the country I believe the situation is improving. But in some sections it is still difficult to obtain safe milk. However, I feel in some small way that I have contributed indirectly to better health in at least one part of our land. Steps have been taken to remedy the situation in that state where I was living — and as a result of my illness. Today the law is severe — all milk must be pasteurized. One thing, however, still puzzles me even now. Why in a state where pasteurization was not enforced and which was crawling with this illness were no tests made for a mysterious febrile illness? And why in a city like Boston where pasteurization is required by law, did it take only five days to diagnose my illness? I draw no conclusions. Let the facts speak.

May Almighty God bless all medical folks, especially the good doctors and nurses in and around the Boston hospitals and the specialist in the deep south who sent me there, and return to them a hundred fold that mercy, kindness and consideration so long shown me.

Lynn, Massachusetts

BERNARD APPEL, M.D.

BOOK REVIEW

The Uncommon Heart Diseases. By Nathaniel E. Reich, M.D., F.A.C.P., F.C.C.P. 8°, cloth, 516 pp., with 110 illustrations and 35 tables. Springfield, Illinois: Charles C Thomas, 1954. $10.50.

The word "uncommon" is a relative term, having at least temporal and geographic qualifications. The selection of subjects for discussion in such a volume as this depends on the choice of cardiac diseases lying somewhere between the "frequent" and the "unique" and between those now appearing in the United States and in other parts of the world. Clearly, the author confines his interest mainly to the Americas and perforce to bibliographies, because of the rarity of the conditions. One searches in vain for the endocardial fibrosis of the natives of Uganda or the epidemic dropsy of Bengal.

The chapter entitled "Non-structural Cardiovascular Abnormalities" includes the effects of exercise, atmospheric pressure, the digestive system, anesthesia, surgery, pregnancy and electric shock.

Other chapters discuss trauma, tumors, "collagen diseases," acute nonspecific myocarditis and pericarditis, chronic constrictive pericarditis, syphilis of the myocardium and valves, tuberculous myocarditis, mycotic infections of the heart, cardiac diseases of parasitic origin, cor pulmonale, nutritional disturbances and vitamins, metabolic disorders, blood dyscrasias, neuromuscular diseases, drugs, electrolytes and toxins, nonarteriosclerotic diseases of the coronary arteries and miscellaneous diseases of the myocardium, pericardium and veins.

One should perhaps not cavil at the inclusion of some routine material, such as the treatment of cardiovascular syphilis, but it is surprising to find in a book published in 1954, after a note on shunt operations for mitral stenosis, "Harken, Bailey and Potts have each advocated other surgical approaches to the problem of mitral stenosis. The ultimate superiority of any of these methods await [*sic*] further studies."

The book has value as a source for one wishing an introduction to the literature of the relatively bizarre; however, the limitation of references has resulted in some important omissions, such as that of Warburg's monograph on cardiac trauma. The occurrence of pericarditis during nonfatal renal failure is not noted. Recurrent pulmonary embolism is not clearly recognized as a common cause of chronic cor pulmonale. The increasingly important condition of fibroelastosis of the endocardium is not mentioned. The geographic distribution of sarcoid is not indicated.

The volume is uncomfortably sprinkled with spelling errors and marred by the use of the word "regime" where "regimen" is intended in describing therapy.

The book can be recommended as a good beginning in the systematic collection of information on the influence on the heart of a multitude of unusual conditions. Such a collection, presumably, can never be complete.

HOWARD B. SPRAGUE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Nervousness, Indigestion and Pain. By Walter C. Alvarez, M.D. Popular edition, 8°, cloth, 235 pp. New York: Hoeber and Brothers, 1954. $3.50.

The original edition of this special book was published in 1943. This popular edition has been written in simple language for lay readers.

Diet Manual of the Jewish Hospital of Brooklyn, 1954. Edited by Charles Solomon, M.D., Nanette D. Robertson, M.A., and Miriam C. Tekulsky, B.S. 8°, cloth, 87 pp., with 5 tables. New York: American Book-Stratford Press, Incorporated, 1954.

This special diet manual is designed for the use of the physicians, dietitians and nurses of the hospital. It deals with the various types of diets.

Laboratory Techniques in Rabies. By D. d'Antona and others. 8°, paper, 150 pp., with illustrations. Geneva: World Health Organization, 1954. $3.00.

This manual presented for the guidance of laboratory workers is the joint work of 14 specialists in rabies from various parts of the world. The text is divided into five parts on laboratory diagnosis, methods of vaccine production, vaccine potency tests, production of hyperimmune serum and laboratory animals. The text is well illustrated.

Medicine and Science. Lectures to the Laity. No. XVI. The New York Academy of Medicine. Edited by Iago Galdston. 8°, cloth, 159 pp., with 31 figures. New York: International Universities Press, Incorporated, 1954. $3.00.

In this series of six lectures Professor Norbert Wiener, of the Massachusetts Institute of Technology, spoke on "Men, Machines and the World About." The anniversary discourse of the New York Academy of Medicine was given by Dr. David M. Levy, professor of clinical psychiatry at Yale University School of Medicine, on the subject "The Relation of Animal Psychology to Psychiatry." Dr. Hans Selye, of Montreal, spoke on the topic "the Renaissance in Endocrinology," and Dr. Harold G. Wolff on "Stress, Emotions and Bodily Disease." Professor Paul R. Burkholder, of Yale, and Mr. John E. McKeen, president of Charles Pfizer and Company, discussed the quest for and production of antibiotics.

The Treatment of the Alcoholic. By Fritz Kant, M.D., psychiatrist and neurologist, and professor of neuropsychiatry, University of Wisconsin Medical School. 8°, cloth, 133 pp. Springfield, Illinois: Charles C Thomas, 1954. $3.50.

This practical book discusses the aspects of chronic alcoholism, with especial emphasis on treatment. The various types of therapy are considered: medical, psychotherapy and Alcoholics Anonymous. There is a glossary, a selected bibliography and a good index.

Mayo Clinic Diet Manual. By the Committee on Dietetics of the Mayo Clinic. Second edition. 8°, paper, 247 pp., with table illustrations. Philadelphia: W. B. Saunders Company, 1954. $5.50.

The first edition of this manual was published in 1949. This revision has brought the subject up to date, and changes have been made in a number of the dieting programs. There is a good index.

Financing Hospital Care in the United States. Vol. 1. Factors Affecting the Costs of Hospital Care. Edited by John H. Hayes. 8°, cloth, 300 pp., with charts and tables. New York: Blakiston Company, Incorporated, 1954. $4.00.

This is the first report of the Commission on Financing of Hospital Care, consisting of 34 persons. The Commission was instituted "to study the costs of providing adequate hospital services, and to determine the best systems of payment for such services." This report covers the first objective. Two more reports are to follow. The report is comprehensive in scope and should be in all collections on hospital administration.

Biochemical Investigations in Diagnosis and Treatment. By John D. N. Nabarro, M.D., M.R.C.P., assistant physician, Middlesex Hospital. 8°, cloth, 299 pp., with illustrations. London: H. K. Lewis and Company, Limited, 1954. 25s.

This book has been written as a practical guide for hospital residents, and therefore detailed descriptions of laboratory methods have been omitted. Its intention is to show how biochemical tests may aid in diagnosis and in treatment. The text is written from the clinical point of view and is arranged generally by pathologic conditions. There are two indexes; the publishing is excellent.

Cystic Fibrosis of the Pancreas in Infants and Children. By Charles D. May, M.D., professor and chairman, Department of Pediatrics, State University of Iowa College of Medicine. 8°, paper, 93 pp., with 16 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.00. (Publication No. 234, *American Lecture Series.*)

Various aspects of the disease including clinical manifestations, diagnosis and treatment, are covered. The author has surveyed the literature, and a bibliography of 82 references is appended to the monograph, which is well illustrated.

The Doctor Writes: An anthology of the unusual in current medical literature. Edited by S. O. Waife, M.D. 8°, cloth, 175 pp. New York: Grune and Stratton, 1954. $4.50.

The editor has brought together in this collection a series of articles of historical interest published in various periodicals during 1953. There are 17 selections divided into four classes: of men and medicine; looking backward; reading and writing; and art and science. This is a book for the history collection.

NONCLINICAL NOTES

DEUTSCHE MEDIZINISCHE WOCHENSCHRIFT

The *Deutsche medizinische Wochenschrift,* as a contribution toward the removal of the language barrier, in medicine, as least, announces that it is now printing English and Spanish summaries of all original articles published in each issue. The editors hope that this will stimulate, among physicians in other countries who know little German, a livelier exchange of medical information with their German colleagues.

NOTICES

ANNOUNCEMENTS

Dr. Alfred Hollander announces the removal of his office to 130 Maple Street, Springfield 5, Massachusetts, for the practice of dermatology.

Dr. Joseph Thimann, director of the Washingtonian Hospital, announces the removal of his office to 39 Morton Street, Jamaica Plain, Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.

JULY 5–AUGUST 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1099, issue of June 23.

JULY 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.

JULY 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.

AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

AUGUST 30 and 31 and SEPTEMBER 1. New England Health Institute. Page 1010, issue of June 9.

OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

NOVEMBER 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

NOVEMBER 11 and 12. Inter-Society Council. Page 1056, issue of June 16.

NOVEMBER 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JULY 7

THURSDAY, JULY 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Thoracic Conference. Surgery of Diaphragmatic Hernia and Esophageal Diverticula. Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

(Concluded on page xvii)

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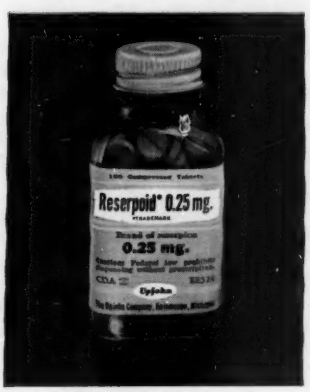

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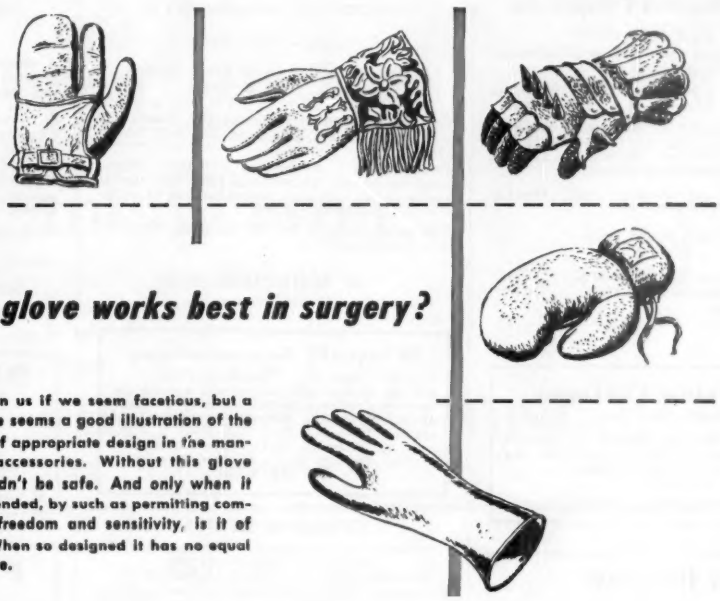

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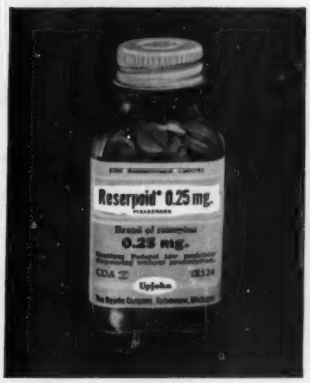

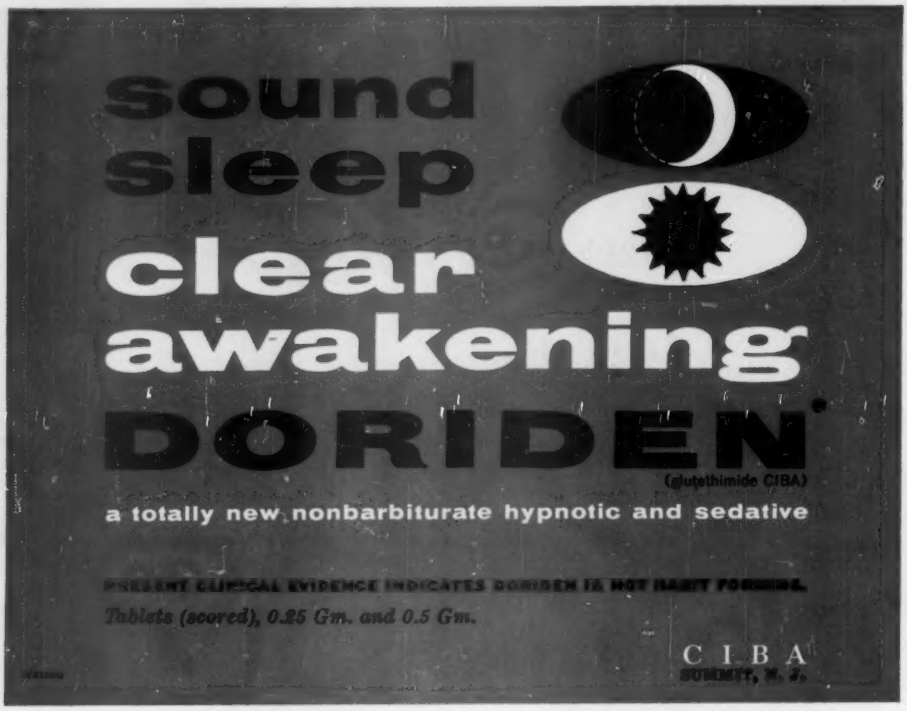

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(Concluded from page 1148)

*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, JULY 8
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, JULY 9
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, JULY 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs, moderator. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Vandam. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.

TUESDAY, JULY 12
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic (Cafeteria), New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, JULY 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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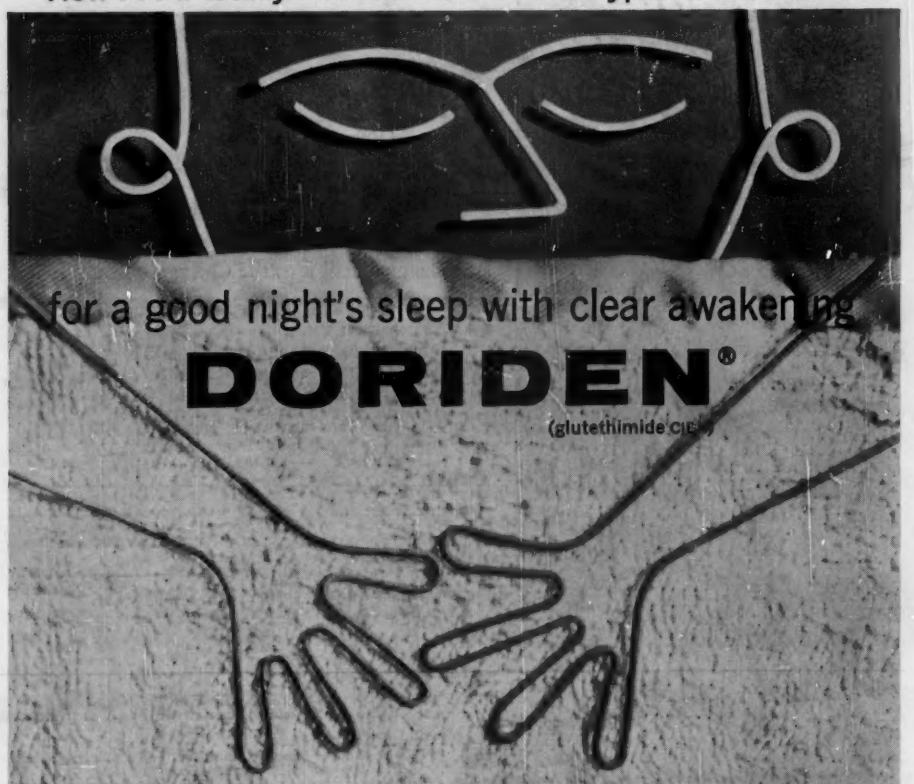

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